

A comparison of Pharmaceutical Regiments Following First Stage Root Canal Treatment

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Dedication

To my beautiful wife Samara. I would not be where I am today without your endless support, sacrifices, and love. This was greatly appreciated and never taken for granted. I am the luckiest man to have you in my life. Even though we were miles apart, I felt you were always right next to me in my heart.

אני לדודי ודודי לי

Abstract

AIM: The purpose of this clinical trial was to investigate the analgesic efficacy of four oral medication groups on postoperative endodontic pain after first stage root canal treatment. The four groups will be

Methodology: Patients presenting to the University of Minnesota emergency graduate endodontic clinic experiencing pain greater than or equal to 3/10 were considered potential candidates. 22 patients were included based on an established inclusion criteria. Following administration of local anaesthesia, a pulpectomy was performed. The patients were administered the following at 4 hour time intervals: (1) 2 doses of Placebo; (2) 2 800mg doses of Ibuprofen; (3) 2 800mg Ibuprofen with Vicodin 325/7.5mg; (4) 1 dose of 550mg Anaprox DS (Naproxen) and 1 dose of Placebo. Patients recorded pain intensity following treatment on a visual analogue scale, Heft parker scale and a baseline four-point category pain scale before and immediately after treatment, then one hour after the initial dose of medication, and one hour after the second dose of medication. The following day, pain was recorded at breakfast, lunch, dinner and bedtime.

Results: At about 24 hours, 27% had moderate to severe pain. All patients showed significant pain reduction after initial root canal therapy. The ibuprofen group showed a rebound in pain the following day. Males had more rebound pain compared to females. Anaprox DS and the

combination of Ibuprofen and Vicodin showed the most pain reduction at all time periods. In our study, the results suggested that pulp vitality had little effect on post operative pain.

Conclusion: Primary endodontic treatment will greatly decrease the pain felt by the patient. High doses of Ibuprofen followed by an abrupt stop might lead to a rebound in pain. Tooth vitality did not seem to affect post operative discomfort, nor did patient gender. More research using this model and analgesic combination is necessary to ensure statistically significant results.

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A COMPARISON OF PHARMACEUTICAL REGIMENS FOLLOWING FIRST STAGE ROOT CANAL TREATMENT

Pain is defined as an unpleasant sensory and emotional experience associated with potential or actual tissue damage (International Association for the Study of Pain 1994). Dental pain in general and toothache pain specifically is one of the key predictor of patients seeking dental treatment (Locker and Grushka 1987), other than regularly scheduled check-ups. Dental pain has been shown to occur quite frequently, with nearly 15 percent of adults in the United States experiencing toothache, oral sores, jaw joint pain, facial pain, or burning mouth in a six month period (Lipton et al 1993). These rates were comparable to rates seen in the United Kingdom and Canada (Shepard et al 1999, Locker and Grushka 1987). Dental pain can interfere greatly in the patient's life, making sleep and work nearly impossible. Every year in the United States approximately 15 million working days are lost due to dental pain (Taylor and Curran 1985).

One of the main objectives of endodontic therapy is to alleviate these patients from pain. Continued pain between appointments can be a considerable problem for patients and endodontists alike. Despite

many advances in the field, the incidence of mild inter appointment pain has been reported up to 30 percent of the time and 15.7 percent for severe pain (Harrison et al 1983). Postoperative pain was more likely to occur in these patients within the first twenty four hour period following treatment (Harrison et al 1983). Patients presenting with extreme preoperative levels of pain were more likely to have a similar degree of pain both operatively and postoperatively (O'Keef 1976). Thus, it is critical for the clinician to minimize or prevent pain by following appropriate treatment regimens supplemented with analgesics where indicated (Menhinick et al 2004).

Even with many advances in endodontic therapy and an increased knowledge of pulpal morphology, histology and immunology, a large percentage of patients still report pain after endodontic treatment. Seltzer and Bender in 1961 found a 40% incidence of post operative pain among 698 patients. Georgopoulou in 1986 had similar findings, with 43% of the 245 patients experiencing pain after endodontic treatment. Numerous studies have shown that this pain following treatment is usually the highest the first 24 hours post treatment (Harrison et al, 1983, Liesinger et al, 1993, Marshall and Liesinger 1993, Torabinejad et al 1994).

There are numerous etiologic factors associated with odontalgia, but tooth pain is usually caused by either noxious physical stimuli, or a release of inflammatory mediators that stimulate terminal endings of afferent nerve fibers (Chiu et al 2012). A release of inflammatory mediators such as prostaglandins, leukotrienes, bradykinin and serotonin activates sensitive nociceptors surrounding the tooth, and is thought to be the major cause of pain (Menhinick et al 2004, Johnsen et al 1983). This leads to both the central and peripheral mechanisms of hyperalgesia which will increase the perceived magnitude of a painful stimulus (Dubner and Bennet 1983). These processes can be controlled through root canal treatment and or the use of anti-inflammatory agents (Menhinick et al 2004). One such medication is acetaminophen whose mechanism of action is not fully understood. However it is known that it is a weak inhibitor of peripheral prostaglandin synthesis (Bjorkman et al 1994). Acetaminophen is also known to be in some way active in the central nervous system via the inhibition of central hyperalgesia induced by pain producing neurotransmitters (Aminoshariae and Khan 2015, Bjorkman et al 1994).

Ibuprofen is one of the most commonly used non-steroidal anti-inflammatory drugs (NSAID) (Menhinick et al 2004, Cooper et al 1993). These drugs inhibit prostaglandin synthesis by decreasing the activity of cyclo-oxygenase enzymes (COX) which exists in two isoforms COX 1 and COX 2. COX 2 is released with tissue injury, which is induced rapidly, (in 1-3 hours) and can be detected in high concentrations in macrophages, monocytes, leukocytes in response to mediators of inflammation (Cooper et al 1993, Arslan et al 2011). Hydrocodone is an opioid used for analgesic, antitussive, antihypertensive, sedative and hypnotic properties. It is metabolized in the liver into its primary active compounds morphine and codeine-6-glucuronide, where it then binds to μ -opioid receptors (Morse et al 1987, Garoulis et al 2012). The combination of acetaminophen and an NSAID has demonstrated improved pain control compared with either drug used separately in the literature for patients with various pulpal conditions (Menhinick et al 2004). There have been no controlled dental studies that make the comparison between the combination of hydrocodone/acetaminophen with ibuprofen, ibuprofen alone and or naproxen alone.

The purpose of this clinical trial is to investigate the analgesic efficacy of four oral medication groups on postoperative endodontic pain after local anesthesia with either lidocaine 2% with epinephrine 1:100000 or a long acting local anesthetic (bupivacaine 0.5% with epinephrine 1:200000). The four drug groups include a lactose placebo, 800 mg ibuprofen, Anaprox DS (550 mg naproxyn sodium), or acetaminophen/hydrocodone (Vicodin 325 mg/7.5 mg). The difference in postoperative analgesic efficacy will be measured using the VAS (100 mm scale), Heft-Parker (170 mm scale with descriptors) , and Categorical (no pain, mild pain, moderate pain, severe pain) pain scales over 36 hours.

HYPOTHESES:

The null hypothesis of this research project is that there will be no difference between the groups in pain control. That is, the root canal intervention alone will be enough for pain relief. The Alternate hypothesis is that there will be a significant decrease in the level of pain between the placebo group versus medicated groups. Furthermore, there will be a difference between the different drug groups.

MATERIALS AND METHODS:

This study was approved by the University of Minnesota Institutional Review Board (IRB). Patients were selected from those that presented to the University of Minnesota College of Dentistry's urgent care clinic. Potential candidates presented with moderate to severe spontaneous pain of odontogenic origin with a rating of 3 or higher on a 10 point scale. Following assignment to a graduate endodontic resident, the patients were given further information about the study, and strict inclusion criteria was applied. Inclusion criteria will be;

1. Patient greater than 18 years of age but less than 65
2. No pain medication taken within the last 4 hours.
3. No allergy to NSAIDS, acetaminophen or local anesthetics
4. No gastrointestinal or kidney disorders
5. Spontaneous pain >3 on a 10 point scale
6. Patient requires a root canal treatment
7. Patient has an American Society of Anesthesiologists (ASA) I or II medical history

8. Patient has given informed consent.

9. Patients are not pregnant.

10. No history of opioid abuse.

Patients were divided based on the type of local anaesthesia used; either two carpules of 2% Lidocaine with epinephrine 1:100,000 3.4 ml, or two carpule of a long acting local anesthesia, 0.5% Bupivacaine with epinephrine 1:200,000 3.6 ml. The treating dentist could also use one additional carpule of Lidocaine, despite the group, should it be necessary. If local anaesthesia is not obtained at this point, the patient will be eliminated from the study, and given additional local anaesthesia to complete the treatment.

Patients will be further subdivided into the following drug groups:

1. Anaprox DS (naproxyn sodium) 1st dose, Placebo 2nd dose
2. Placebo 1st dose, placebo 2nd dose
3. Ibuprofen 800mg 1st dose, Ibuprofen 800 mg 2nd dose
4. (Ibuprofen 800 mg + Vicodin (acetaminophen/hydrocodone) 1st dose, (Ibuprofen 800 mg + Vicodin) 2nd dose

Patients consenting to be in the study were given local anaesthetic that had been previously randomized with label covered and provided within the patient packet for the treating dentist. Pain evaluation forms were also be provided in the packet. Standardized endodontic

procedures were performed by the graduate endodontic residents under rubber dam isolation. Resident used rotary nickel titanium instruments in a modified crown-down technique and stainless steel hand instruments as necessary. The cleaning and shaping was done to at least a size 25 master apical file to within 0.5 - 1.0mm of the estimated working length determined by apex locators and verified by radiographs. Copious irrigation with 5.25% sodium hypochlorite was used between each file. Once instrumentation was completed, the canals were dried with paper points, and an intra-canal medicament of Calcium Hydroxide (UltraCal X5, Ultradent USA) and a cotton pellet was placed in the access cavity, which was then restored with 3mm of Cavit.

When the patient neared completion of the endodontic treatment, a prescription written for the IRB study and was presented to the pharmacy, which will then fill the prescription with a randomized code known only to the Investigational Drug Services (IDS) pharmacy at the UMN. Two clear, unmarked, indistinguishable vials were provided by the pharmacy for each patient labelled "1st dose" and "2nd dose". The first dose was taken 1 hour after dental treatment had been completed when the patient is safe at home, and the 2nd dose 4 hours later. The vials contained the appropriate randomized drugs from the drug groups

above in the generic form. The IDS pharmacy provided a 24 hour, 7 day a week phone service number if the patients experienced pain that was not managed by the test drug. The patient would have been un-blinded, and given the appropriate rescue medication.

Also provided in the packet was a pain diary that contained two pain scales (VAS and Heft-Parker scale) and a categorical scale which was simply descriptive of the pain intensity on a four point scale from “no pain” to “severe pain. There was an area for the patient to record any side-effects. The diary was 8 pages long, designed so patients can make entries pre-treatment, immediately post treatment, then 1 hour following the 1st dose of medication, 1 hour following the second dose (6 hours later), and then the following day at breakfast, lunch, dinner and bedtime. Had any medication been taken the following day, the patient had a place to indicate which medication taken, and the dose. To compare treatment groups without considering initial VAS, a repeated measures analysis of variance was used, where the random effect is subject and the fixed effects are drug, group and time, and their interaction. To compare treatment groups while also considering initial pain scale, a mixed linear model was used, a generalization of a repeated-measures ANOVA. If group by time interaction is significant, sepa-

rate post-hoc tests will be done comparing the medication groups at each time point.

Literature Review

Dental pain is one of the leading causes of people seeking dental treatment, with 12% of Americans suffering with odontalgia annually (Anderson and Thomas 2003; Gilbert et al 2003). Approximately 85% of all dental emergencies arise as a result of pulpal or periapical disease, which would necessitate either extraction or endodontic treatment to relieve pain (Hasler and Mitchel 1963). Awareness of pain involves its detection, which is a function of the peripheral sensory neurons, then the processing which involves the selective activation of specific and related central nervous system pathways that are dependent on initial processing done with the medullary and spinal dorsal horns. The final step of pain awareness is perception, which is the result of activity in the more rostral brain regions such as the cerebral cortex (Hargreaves 2013). All three of these steps are responsible for the multidimensional aspect of pain that includes pain both as a sensation and emotion for the patient. For clinicians, the initial challenge is to understand the biological process resulting in pain.

The pulp is one of the most densely innervated tissues in the body, containing both sensory afferent fibres and sympathetic fibers that modulate blood flow (Trowbridge 1986). The sensory and post-ganglionic sympathetic nerves that innervate the dental pulp originate in the trigeminal and superior cervical ganglia, respectively, and enter through the apical foramen. The nerve bundles pass coronally through the radicular pulp along with blood vessels, fanning out once reaching the cell-rich zone of the pulp. Nerves are classified based on their diameter, conduction velocity and function (Itoh 1979, Johnsen 1985). In the pulp, we find two types of sensory nerve fibers; the myelinated (A fibers) and the unmyelinated (C fibers). The A fibers consist mainly of the A beta and A delta fibers. The A beta fibers are larger, and have faster conduction velocity when compared with the A delta fibres. Approximately 90% of the myelinated fibers are A delta (Olgart 1989). Branches of the nerves will give rise to the network called the subodontic plexus in the peripheries of the pulp, where the fibres terminate as free nerve endings (Trowbridge 1986). These free nerve endings will pass between the odontoblast cell bodies and enter the dentinal tubules (Byres et al 1980). These intratubular nerve endings are most numerous in the pulp horn, where nearly 40% of tubules will contain

nerve fibres (Byres 1984). Intradental A and C fiber groups are functionally different and can be activated separately by certain external stimuli with A fibers responsible for the sensitivity of dentine and the mediation of sharp pain brought on by light stimulation (Narhi et al 1992, Olgart et al 1989, Nair 1995). Intradental C fibers are activated only if the external stimuli is able to reach the pulp proper. Their activation may contribute to the dull pain induced by intense thermal stimulation, or that associated with pulpal inflammation. In the pulp proper, only C fibres can be activated by histamine and bradykinin seen in inflammation (Narhi et al 1992).

Inflammation seen in diseased dental pulps leads to the activation of pulpal nociceptors and odontogenic pain (Woolf 1999, Willis 1985, Hargreaves et al 2001). This pain is thought to arise from the activation of unmyelinated nociceptors due to the distribution of C fibers in the dental pulp, their responsiveness to inflammatory mediators, and similar perceptual qualities of pain associated with C fiber activation (Hargreaves 2013, Ahlquist et al 1985). Stimuli will cause depolarization of nociceptors sufficient to generate an action potential by means of opening voltage gated sodium channels. The information from this action potential will be sent not only to the central nervous

system, but will also be sent in the reverse direction back into the tissue antidromically (Keiser and Byrner 2011). This is also referred to as axon reflex, and will stimulate the release of pro inflammatory neuropeptides such as substance P (SP), calcitonin gene-related peptide (CGRP) from the pulpal nerve fibers (Hargreaves and Swift 1993).

CGRP has been shown to cause vasodilation, while SP increases vascular permeability acting directly on arterioles and venules, and indirectly stimulates the release of histamine and eicosanoid production by mast cells. The levels of substance P in pulp tissues diagnosed with irreversible pulpitis are seen to be increased eight fold (Bowles et al. 2003). Prostaglandin, which is produced after the release of eicosanoid has been shown to be present in higher concentrations in acute periradicular lesions of inflamed teeth (McNicholas et al. 1991) as well as substantially increasing the stimulatory effect of bradykinin (Goodis et al 2000).

The action potential is propagated along a peripheral trigeminal nerve to the primary afferent neuronal cell body located in the trigeminal ganglion, and then into the central nervous system (Hargreaves et al 2001). Impulses carried by the trigeminal nerve will enter directly into the brain stem in the region of the pons to synapse with the second or-

der neurons in the trigeminal spinal nucleus. This region is structurally very similar to the dorsal horn of the spinal cord, and is sometimes referred to as the medullary dorsal horn. The caudal extent of the trigeminal nucleus will merge with the dorsal horn at the upper cervical level (Hargreaves and Goodis 2001).

The trigeminal spinal tract nucleus is divided into three regions; the subnucleus oralis, subnucleus interpolaris and the subnucleus caudalis. Primary afferent neurons innervating dental pulp terminate in all the different subnuclei located within the ipsilateral trigeminal sensory nucleus, including prominent projections to the subnucleus caudalis (Sjoqvist 1938). The caudal region plays a critical role in the modulation and transmission of nociceptive information from the trigeminal sensory nucleus. The impulse is then carried by the second order neurons across the brain stem to the anterolateral spinothalamic pathway and ascends through the reticular formation to the thalamus. The reticular formation will control the overall activity of the brain by either enhancing or inhibiting the impulses to the brain. The impulse will finally ascend to the cortex for interpretation and evaluation. Output to higher brain regions can be increased, decreased or misinterpreted from

incoming activity (Okeson 1995, Malamed 1990, Henry and Hargreaves 2007).

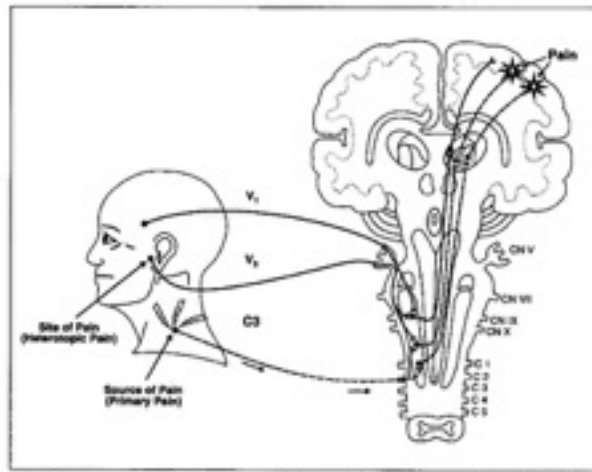


Figure 1: Graphic illustration of the convergent effect of nociceptive input on the trigeminal spinal tract nucleus. The C3 will converge on the trigeminal neuron, creating nociceptive input ascending onto the higher centres. (Henry and Hargreaves 2007)

For many years, it was suggested that there is a circuit system in the CNS that can modulate incoming pain information. The first pain modulatory mechanism, called the ‘Gate Control theory’ was proposed by Melzack and Wall. The concept is that non-painful input closes the gates to painful input, thus preventing pain sensation travelling to the CNS (Melzack and Wall 1964). It is now accepted that there is a powerful inhibition of pain-related information in the spinal cord. Circuit interneurons are an important part of the trigeminal sensory nuclei as

they will ultimately regulate the transmission of nociception signals from the primary afferent fibers to projection neurons (Hargreaves 2012). Inhibitory influences are provided by GABA or opioid within the synaptic vesicles located in the primary afferent axon terminals at axoaxonic inhibitory synapses, providing presynaptic inhibition of primary afferent input (Hargreaves 2002). Another integral part of the trigeminal sensory nuclei are the descending neurons which modulate the transmission of nociceptive information within the other caudal neural components via endogenous opioids and serotonin (Millan 2002, Hargreaves 2012). The analgesic action of some selective serotonin reuptake inhibitors and opioids may involve activation of these descending neurons (Hargreaves 2012). Endogenous opioid peptides possess many of the properties of exogenous opioids such as morphine and codeine, and are found at several levels of pain suppression system (Hargreaves et al 1986). Endogenous cannabinoid system is another modulatory system that can inhibit the central terminals of C fibres. There are ten times more cannabinoid receptors than opioid in the CNS (Hohmann and Herkenham 1999) and cannabinoid receptors in the pulp which act to inhibit peripheral terminals of unmyelinated nociceptors (Hohmann and Herkenham 1999).

Microbial infections are the most prevalent aetiology of pulpal inflammation followed by trauma (Hargreaves 2012). Inflammation evoked by microorganisms is a complex response that involves recognition of antigenic molecular patterns, and the coordinated release of multiple classes of inflammatory mediators such as bradykinin, IL1 and PGE₂ to name a few (Hargreaves and Hutter 2002). Lipopolysaccharide (LPS) is the most prominent microbial antigen in dental infections due to the high representation of gram negative bacteria (Hashio-ka et al 1992, Siqueira et al 2004). LPS has the ability to diffusing and reaching the pulp faster than bacteria (Khabbaz et al 2001), thus alerting of the host of incoming bacterial infection quite early. Vasoactive peptides such as CGRP and SP will initiate and amplify the pulpal inflammatory reaction, also known as neurogenic inflammation. These peptides will act in conjunction with the aforementioned cytokines released by dendritic cells to activate the innate immune response by specific receptors expressed on the plasma membrane of cells of innate immune response, namely the toll-like receptors 4 (TLR4) (Diogenes et al 2011). TLR4 is also expressed in dental nociceptors and neuronal recognition of this bacterial component activates and sensitizes these dental pain sensing fibres, thus increasing nociceptive signals and release of pro inflammatory neuropeptides (Diogenes et al 2011, Ferraz

et al 2011). Primary afferent terminals in the dental pulp and periodontal tissues can directly sense the bacterial presence by the activation of TLR4 and subsequent activation of its associated nociceptors, leading to an alerting pain signal and activation of the immune defence (Jiang et al 2006).

The earliest pulpal response to bacterial infection or antigens includes the infiltration of polymorphonuclear leukocytes (PMNs) and monocytes, with PMNs being the most abundant type of phagocytes (Bergenholtz and Lindhe 1975, Takahashi 1998). In PMNs and reticulocytes, arachidonic acid is metabolized by the lipooxygenase enzyme to produce a series of products called leukotrienes. Leukotrienes have been found to be potent chemotactic and enzyme-releasing agents for leukocytes, and have been associated with smooth muscle constriction and broncho-constriction (Samuelsson and Hammarstrom 1980). Leukotrienes have also been shown to have 100-1000 times the power of prostaglandins and histamine in promoting vasodilation and vascular permeability (Samuelsson 1983). In addition to the pro-inflammatory actions of leukotrienes (chemotaxis, vasodilation, and vascular permeability), this family of

compounds has been shown to prolong the excitation of neurons brought about by the aforementioned neurogenic inflammation, thus possibly reducing pain threshold (Madison et al 1992).

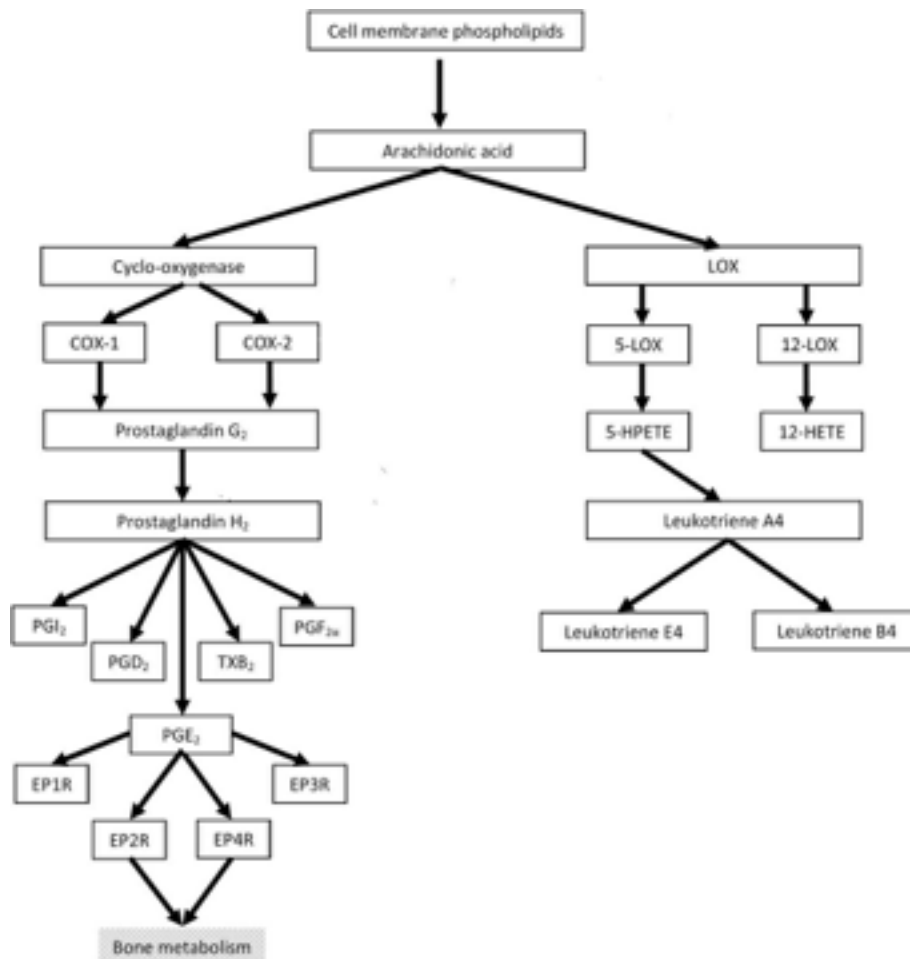


Figure 2: Schematic Representation of the 5-Lipoxygenase enzyme metabolic pathway.

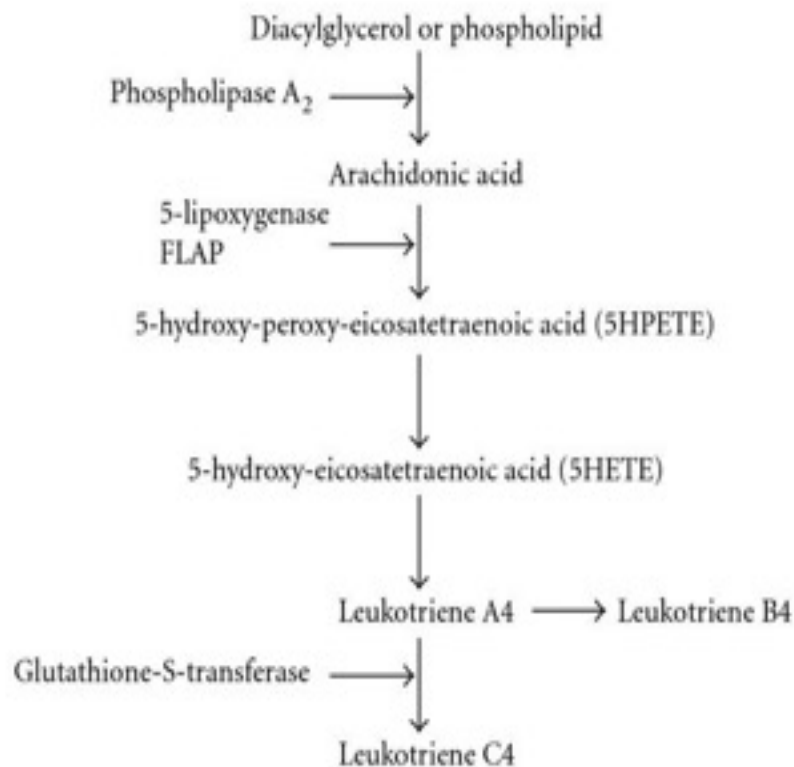


Figure 3: The Eicosanoid Synthetic Pathway

Cyclooxygenase (COX) is an enzyme that is responsible for the formation of prostanoids, such as prostaglandins and thromboxane.

Two of the most common types of COX enzymes are COX-1 which is present in most tissues and COX-2 which is found primarily at sites of inflammation. The COX-1 enzyme is distributed throughout the body and produces prostaglandins which have a protective role that includes preventing gastrointestinal ulcers, regulating platelet action, and con-

tribute to kidney function. Prostacyclin and PGE₂ reduce gastric acid secretion, exert direct vasodilator action on the vessels of the gastric mucosa, and stimulate the secretion of viscous mucous as a protective barrier against gastric ulcers. In platelets, COX-1 activity produces TXA₂, causing aggregation of the platelets and prevention of inappropriate bleeding. PGE₂ and PGI₂ promote vasodilation in the kidney, thus preventing kidney ischaemia. PGE₂ also inhibits reabsorption of sodium and chloride from the ascending loop of Henle in the kidney, and attenuates reabsorption of sodium by vasopressin in the collecting ducts, thus increasing urine flow (Vane and Botting 1998). COX-2 is an inducible enzyme that increases in inflammation. Byproducts include prostaglandins in migratory and resting cells. Little or no COX-2 is found in resting cells, but expression can be increased by exposure of these cells to bacterial lipopolysaccharides or cytokines during inflammation (Vane and Botting 1998).

Hyperalgesia, an increase in the perceived magnitude of painful stimuli, can develop in response to changes in the pain system. These changes can be seen within seconds of the appropriate stimuli (Hargreaves et al 2001, Sessle 2000). Hyperalgesia occurs not only in areas of inflammation and tissue injury (Primary hyperalgesia), but also in

adjacent areas (Secondary hyperalgesia) (Raja et al 1984). Allodynia, a reduction in the pain threshold so that previously non-noxious stimuli are perceived painful, can also arise from these changes in the pain system (Pacheco et al 2011). In a recent prospective study, mechanical allodynia was detected in 56% of those diagnosed with necrotic pulps, and 67% of those with irreversible pulpitis (Olgart et al 1989). Central mechanisms of allodynia and hyperalgesia have been proposed, and can lead to a pain state called central sensitization, marked by an increased excitability of central neurons (Woolfe 1996). Activation of pulpal neurons produces central sensitization due to the release of glutamate and SP, and an increased expression of NMDA receptors in both the trigeminal nuclei and thalamus (Chiang et al 1998, Sunakawa et al 1999). Allodynia and hyperalgesia can persist after the removal of the sensory input from inflamed tissue, which can explain why up to 80% of patients who experience pain before endodontic treatment will report pain after (Marshall and Walton 1984, Marshall and Liesinger 1993). Patients with moderate or severe pain usually report greater pain levels for 3 days after endodontic treatment (Hargreaves KM et al 2002). It has been recently reported that the overall incidence of pain six months post endodontic treatment is 5.3% with 3.4% of nonodontogenic origin (Nixdorf et al 2010).

It is impossible to provide effective dental care without the use of local anaesthetics. These drugs interrupt neural conduction by inhibiting the influx of sodium ions after diffusing through the neural membrane and enter sodium channels, preventing them from assuming the open “active” state (Becker and Reed 2006). Thus, the resting potential of the nerve is altered which alters the threshold potential at which the nerve will fire, decreasing the rate of depolarisation, and prolonging the repolarization phase. There are two different families of local anaesthetics, defined by the chemical linkages between the groups; those with ester and those with amide linkages. The amide linkages are more popular and in wider use due to issues with allergies seen in the ester anaesthetics (Becker and Reed, 2006). Local anaesthetics have pK_a s that range between 7.5 to 8.1 thus making them weak bases (Malamed et al 2012). The onset and duration of local anaesthetics are highly variable and specific for each drug, and affected by a number of factors. The most significant of these factors being the pK_a , pH of the solution, lipid solubility, the concentration of active ingredient of the drug and the use of vasoconstrictors such as epinephrine (Malamed et al 2012). Two common local anaesthetics used are bupivacaine and lidocaine. Bupivacaine is much more lipid soluble

compared to lidocaine, thus it is more potent and necessitating a lower concentration (0.5% versus 2.0%). Bupivacaine also has greater protein binding, and thus longer duration versus lidocaine (Bacsik et al 1995). When comparing the long acting bupivacaine anaesthetic with the moderately acting lidocaine, Moore and Dunskey found no difference in the onset and profundity of anaesthesia. It was discovered, however, that there was a significant decrease in postoperative pain in the bupivacaine group (Moore and Dunskey 1983).

Many studies have shown the efficacy of definitive dental treatment, such as pulpotomies, pulpectomies, occlusal adjustment and trephination to reduce acute pain. Pulpotomies, the removal of the coronal portion of a vital pulp as a means of preserving vitality, have been shown to reduce pain symptoms in 88% of patients 24 hours after the initiation of treatment (Hasselgren et al 1989). Pulp debridement, the complete removal of the pulp tissue, is the treatment of choice with symptomatic irreversible pulpitis or with necrotic tissue (Doroschak et al 1999, Torabinejad et al 1994, Hasselgren 1989). Pak and White found that one week after endodontic treatment, only 5% still experienced pain, but normally at a substantially minimal level (Pak and White 2011). Preoperative occlusal adjustment has been shown to help

reduce reduced patient pain on biting (Jostes et al 1984), but has little effect on postoperative pain (Parirokh et al 2013, Creech et al 1984). An in vivo study demonstrated that patients presenting with pain, percussion sensitivity, vital pulps and no periradicular radiolucencies would benefit the most from occlusal reduction (Rosenberg et al 1998). Other forms of definitive treatment to decrease pain are incision and drainage and trephination which help reduce tissue pressure. However trephination, a surgical procedure in which there is a perforation of the alveolar cortical plate, has been suggested to have questionable post operative benefit, and might add to the discomfort (Moos et al 1996, Houck et al 2000). The pain relieving benefits of all the aforementioned treatments are believed to be based on reduction in tissue levels of factors that stimulate peripheral terminals of nociceptors or reduce the mechanical stimulation of sensitized nociceptors. These treatments can provide a predictable pain reduction in patients with an endodontic emergency (Doroschak et al 1999).

Even when endodontic procedures are performed to the highest standard, the patient can still suffer with post-operative pain, with up to 40% of patients still experiencing post-treatment pain during the first 24 hours (Harrison et al 1983, Moskow et al 1984, Georgopoulou et al

1986, Oguntebi et al 1992, Liesinger et al 1993, Marshall and Liesinger 1993, Torabinejad et al 1994, Mattscheck et al 2001, Direnzo et al 2002). Pre-treatment and post-treatment endodontic pain is thought to be related to a periapical inflammatory response. Inflammatory mediators from the infected pulp are thought to cause irritation and sensitization of periapical tissue (O'Keefe 1976, Harrison et al 1983, Marshall and Liesinger 1984, Genet et al 1987, Torabinejad et al 1988, Walton and Fouad 1992, Torabinejad et al 1994, Mattscheck et al 2001).

There have been many factors in the literature that are linked with post-operative pain following a non-surgical root canal treatment. One of the major predictors of post-treatment endodontic pain is the presence and duration of pre-treatment pain or swelling (O'Keefe 1976, Harrison et al 1983, Walton and Fouad 1992, Mattscheck et al 2001, Ng et al 2006). Patients that had previously experienced painful treatment in the orofacial region were approximately 3.8 times more likely to have pain after a root canal treatment (Polycarpou et al 2005). Molar teeth have been implicated also, especially if in the mandible (Walton and Fouad 1992, Ng et al 2006). Studies have been contradicting when considering preoperative tooth vitality as a factor, with some suggesting there is greater discomfort in necrotic teeth (Walton

and Fouad 1992) and others suggesting that pulpal diagnosis has no significance, especially if apical patency is maintained (Arias et al 2009). Some studies found that females were much more likely than men to develop post operative pain (Torabinejad et al 1988, Ng et al 2004, Polycarpou et al 2005). However, other studies did not find gender differences in prevalence, and suggested that those studies that did were biased as ladies were more likely to keep an appointment for pain (Locker and Grushka 1987, MacEntee et al 1993). Post-treatment pain can occur in response to instrumentation and extruded bacteria/necrotic tissue (Seltzer and Naidorf 1985, Torabinejad et al 1988, Siqueira et al 2004). While pain levels tend to diminish after 24 hours, it is perfectly understandable for a patient to desire minimal to no pain during and after treatment. To aid in the control of post-treatment pain, an analgesic agent or a combination of anti-inflammatory/analgesic agents can be used. Thus, it is important to consider pharmacological aids to help alleviate post-operative pain.

Ibuprofen is the prototypical Non-steroidal anti-inflammatory drug (NSAID) and represents the gold standard against which new analgesic agents are evaluated (Huber and Terezhalmay 2006). The analgesic mechanism of action common to NSAIDS such as Ibuprofen

and Naproxen is their capacity to limit hyperalgesia by inhibiting the activity of COX-1 and -2, and thereby the synthesis of inflammatory and hyperalgesic prostaglandins within the peripheral tissues (Mehrvarzfar et al 2012). The inhibition of both COX-1 and COX-2 reduces inflammation and pain by blocking the previously discussed mechanisms, and also inhibits activation of the transcription factor nuclear factor-kappa Beta (NF- κ B), which is critical for the inducible expression of multiple cellular and viral genes involved in inflammation and infection, including Interleukins -1 and -6 (IL-1, -6), and adhesion molecules (Kopp and Ghosh 1994).

However, COX-1 also have protective actions in the body which are also inhibited when taking NSAIDs. Most NSAIDs developed are nonselective COX inhibitors, meaning that they block both COX-1 and COX-2 (e.g. Diclofenac, Diflunisal, Ketorolac, Naproxen, and Ibuprofen). Non-assertive NSAID's have been introduced as selective COX-2 inhibitors; these include Celecoxib, Valdecoxib, and the recently discontinued Rofecoxib. The selective COX-2 inhibitors block production of the inducible COX-2 products and their deleterious effects, while avoiding the unwanted side effects of COX-1 inhibition such as gastro-intestinal bleeding (Vane and Botting 1998). Michels et

al in 2012 found the relative risk of any GI bleeding-related event ranged from 1.1 to 2.4% for users of over the counter Ibuprofen. No studies have demonstrated that COX -2 inhibitors had better pain control compared to non-selective NSAIDs, however, it has been shown that COX-2 specific inhibitors will have a longer duration of action (Huber and Terezhalmay 2006). It is important to note that the actions of lipooxygenase are not inhibited by COX-2 selective NSAIDs, and can only be limited via steroid intervention by the inhibition of the enzyme phospholipase A₂ (Becker 2005). COX -2 inhibitors have been shown to increase the risk for cardiovascular events in atherosclerotic arteries, as more Thromboxane A₂ is produced, which promotes platelet-dependent thrombosis (Becker 2005). A study which compared patients taking selective COX-2, rofecoxib, versus a non-selective COX Naproxen for 6 weeks showed people on the rofecoxib had elevated blood pressure (Sowers et al 2005).

The non-selective NSAID ibuprofen was originally approved for prescription in 1974 with the brand name Motrin. It was approved for over the counter sales in 1984 with a lower daily recommended dosage compared to the prescription product (200 mg every 4-6 hours vs. 400-800 mg every 4-6 hours) with a maximum daily dose of

3200mg (FDA Non-prescription use of ibuprofen and the risks of gastrointestinal and renal toxicity 2002). The time of maximum plasma concentration for ibuprofen is 0.5-3 hours, with an elimination half-life of 2-3 hours (drugs.com). Naproxen was originally marketed as the prescription only drug Naprosyn in 1976, while Naproxen sodium was marketed under the name Anaprox in 1980. In the United States, the FDA approved its use as an over the counter drug in 1994, usually marketed under various names such as Aleve, Anaprox, Flanax, Proxen and Xenobid. It is available in 250mg to 500mg doses as Naproxen or 275mg to 550mg for Naproxen sodium (250-550 mg twice per day) with a maximum daily dose of 1500mg naproxen, or 1650 mg naproxen sodium (drugs.com). The maximum placental concentration of naproxen is between 3-6 hours, with an elimination half life between 12 - 17 hours (drugs.com).

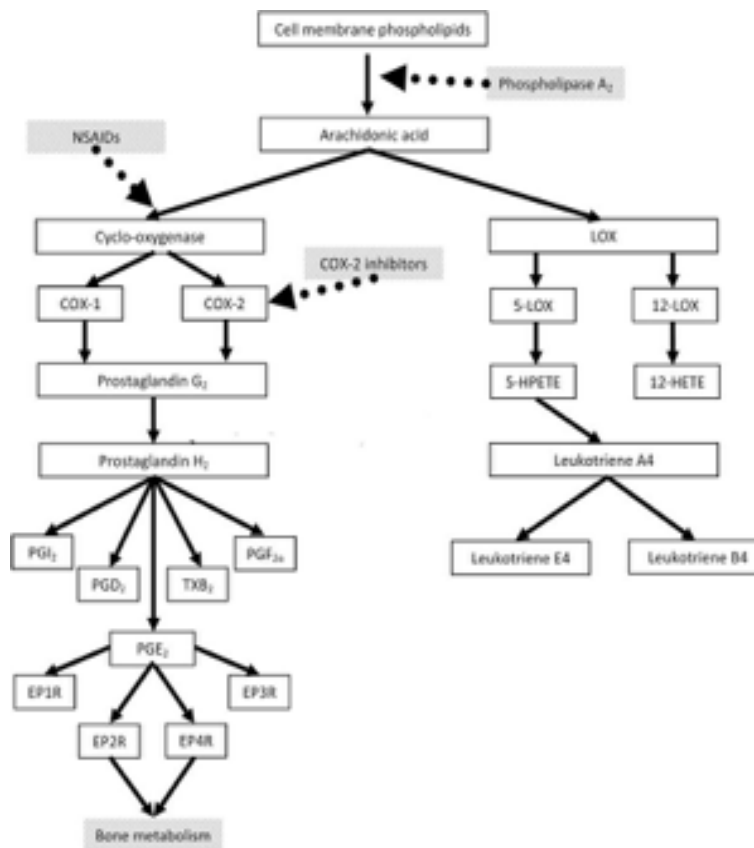


Figure 4: Where NSAID's and COX-2 inhibitors interact in the eicosanoid Synthetic Pathway

Ibuprofen has been shown in numerous studies to be effective in relieving moderate dental pain. Ibuprofen 400 mg has been shown to be superior to placebo four hours after third-molar-impaction surgery (Cooper et al, 1982). The same dosage of ibuprofen has also been shown to be more effective than placebo and acetaminophen 1000 mg following other procedures including extractions, root end resections, biopsy, and deep gingival curettage (Mehlisch 2002). Dionne found that the efficacy of 400 mg ibuprofen in controlling pain following removal of 2-4 impacted third molars was not improved by the addition

of 5 mg of the opioid oxycodone (Dionne, 1999). Naproxen has also shown its efficacy in relieving moderate pain post third-molar-impaction surgery, at a dose of 220mg to 440mg for up to at least 8 hours (Young et al 2013, Li-Wan-Po et al 2013, Moore et al 2011). It has been suggested that there are gender differences in analgesia effects of certain medications, especially in the Naloxone class where females have been shown to have greater analgesia than males over longer periods of time (Ryan et al 2008).

Acetaminophen is one of the most popular analgesics and antipyretic agents in the United States (Guggenheimer 2011). It has been proven to be an effective analgesic, but lacks the anti-inflammatory and anti-platelet effects and gastric irritation common with non-steroidal anti-inflammatory drugs (NSAIDs). It is the only drug in the aniline family that is available in the United States (Aminoshariae and Khan 2015). For many decades, the mechanisms of action of acetaminophen were unclear. It is now known that acetaminophen will block prostaglandin synthesis from arachidonic acid by inhibiting the enzymes COX-1 and -2 when the levels of arachidonic acid and peroxide are low, but have little effect when these levels are high, as seen in severe inflammatory conditions (Aminoshariae and Khan, 2015). Ac-

etaminophen acts centrally and peripherally by inhibiting PGE₂ synthesis. Unlike NSAIDs, acetaminophen also inhibits myeloperoxidase, and may slow the development of disease such as rheumatic disease and atherosclerosis. Acetaminophen also has an antinociceptive effect linked to endogenous opioid, serotonin and cannabinoid neurotransmitter systems. Inhibitors of endogenous opioids, serotonin and cannabinoids will attenuate the antinociceptive effect of acetaminophen (Lee et al, 2007, Dani et al, 2007, Pelissier et al, 1996). This effect of acetaminophen may also be mediated by inhibition of neurotransmitters in the central nervous system by attenuating the nociceptive behaviour of NMDA and SP (Aminoshariae and Khan, 2015). Acetaminophen is absorbed in the small intestine, thus it is influenced by rate of gastric emptying and contents. It has excellent bioavailability, reaching peak plasma concentration within thirty to sixty minutes. Due to low plasma protein binding, it is readily distributed throughout the body (McGilveray, 1972). It is also able to cross both the blood-brain barrier and placental barrier. The maximum plasma concentration of Acetaminophen is between 0.5-3 hours, with an elimination half-life of 2-3 hours ([drugs.com](https://www.drugs.com)).

Acetaminophen is metabolized in the liver, producing a highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), where it is eliminated in urine. After large doses of acetaminophen have been taken or when the patient has existing liver damage, alcohol issues, taking other medications metabolized in liver, or malnutrition, NAPQI may accumulate in the liver in high concentrations, resulting in hepatic damage even with therapeutic doses (Forrest JA, et al 1982, FDA drug safety communication, 2014). Acetaminophen is the leading cause of acute liver failure in the United States, being the cause of nearly 50% of unintentional overdose (FDA drug safety communication, 2014). To address these issues, the FDA centre for drug evaluation and research prepared an internal report that first changed labelling on over the counter packaging in 2009, which then led to manufactures limiting the strength of acetaminophen to a maximum of 325 mg per capsule in 2011. In January 2014 the FDA and manufacturers began to discontinue prescribing and dispensing prescription combination drug products with more than 325 mg acetaminophen until ultimately they were all formally removed from market in March 2014 (FDA drug safety communication, 2014).

Despite the dangers of hepatotoxicity, acetaminophen is still used routinely because of the rarity of adverse effects on health, concurrently used medications and laboratory tests. Systemic reviews and meta-analysis have shown evidence that acetaminophen offers acceptable analgesia that lasts for four hours with minimal effects for acute postoperative pain (Zahrowski, 2011, Barden et al, 2004). Although it is not as effective in relieving acute pain as NSAIDs, it has been shown to provide effective analgesia in about 50% of patients with acute postoperative pain, and is the analgesic of choice when NSAIDs are contraindicated (Zahrowski, 2011).

Narcotic analgesics are a class of analgesics that are useful in treating moderate to severe pain not alleviated by NSAIDs or acetaminophen. Frequently used narcotic analgesics include morphine, hydrocodone, oxycodone, codeine, and meperidine. Hydrocodone and oxycodone are semi-synthetic opioids with multiple actions qualitatively similar to those of morphine. Codeine and morphine occur naturally as a component of the poppy plant and can be recovered from the opium extract of the plant. These analgesics all bind and activate the mu (μ) opiate receptor in the CNS, as does the endogenous opiate beta-endorphin (Hargreaves et al 1987). Opioid receptor types include the mu

(μ), delta (δ), kappa (κ), and sigma (σ) receptors which inhibit adenylyl cyclases, increase intracellular calcium levels, decrease calcium currents, increase potassium currents, and regulate mitogen-activated protein (MAP) kinase second messenger cascade. These actions inhibit neurotransmitter (e.g., SP) release and/or hyper-polarize cell membranes, thus inhibiting neuronal activity (Law et al 2000).

Narcotic analgesics are selective for different opioid receptors and have different activity when bound to these receptors. Activation of the μ receptor produces analgesia, respiratory depression, nausea, sedation, and addiction. Activation of the δ receptor produces analgesia while activation of the κ receptor produces analgesia and sedation. The δ receptor, which has not been associated with an endogenous opioid, is thought to produce immune system modulation, dizziness, light headedness, sedation, dysphoria, and psychotomimetic events such as hallucinations. Morphine, hydrocodone, oxycodone, codeine, and meperidine are full μ receptor agonists, partial δ and κ receptor agonists (Swift and Hargreaves 1993). Certain brand medications such as Vicoprofen, Lortab ASA, and Empirin combine the NSAIDs ibuprofen and aspirin with a narcotic. The effects of an anti-inflammatory agent combined with an analgesic drug working via different mechanisms

proving beneficial in the management of pain. The maximum plasma concentration of hydrocodone is 1 to 1.5 hours, with an elimination half-life of 3-4 hours (drugs.com).

The number of studies on the efficacy of NSAIDS using an endodontic model is limited (Holstein et al 2002). Rogers found that post-instrumentation pain was consistently lower in patients given one 600 mg dose of ibuprofen immediately post-treatment compared to placebo at 6, 12, 24, and 48 hours, but these differences were not statistically significant (Rogers et al 1999). Another study conducted by Torabinejad showed that 400 mg ibuprofen was more effective than placebo in treating postoperative endodontic pain following complete instrumentation. The same study showed that acetaminophen 650 mg, aspirin 650 mg, and Phenaphen #4 (acetaminophen 325 mg + codeine 60 mg) were not more effective than placebo (Torabinejad et al 1994). Menhinick's study showed that a combination of ibuprofen and acetaminophen reduced pain 8 hours post operatively compared to ibuprofen alone and or placebo (Menhenick et al 2004). In a study done by Doroschak conducted at the University of Minnesota, patients treated with fluriprofen and Tramadol reported less pain compared with the placebo group, showing an NSAID/opiate combination in conjunction

with endodontic therapy may be useful in the management of endodontic pain (Doroshak et al 1999).

Extraction of impacted third molars serves as the standard model for testing efficacy of analgesics on dental pain. This model induces pain that is consistent in severity, which allows discrimination between weak and strong analgesics (Urquhart 1994, Ryan et al 2008), and provides the U.S. Food and Drug Administration with accepted evaluations of analgesic therapies (Averbuch and Katzper 2000). However, the oral surgery model does have limitations. Demographically, it tends to enlist a young, healthy, homogenous population seeking elective surgery. It also tests pain of fairly limited range and duration (Mehlisch 2002). The oral surgery model is also based on acute inflammation following a healthy state. In contrast, the endodontic model differs in that patients seeking endodontic treatment vary in age, health status, and preoperative pain presentation. The endodontic model also includes acute inflammatory states following treatment of chronic or acute inflammation.

Pain is a complex perception, having both a sensory and emotional component to it, thus its measurement can be quite problematic

(Chapman et al 1985). The progress in the measurement in pain has been slow due to the fact that pain is a complex perceptual experience that can be quantified only indirectly. Some of the methods used to quantify pain in clinical research are rating scales (Joyce et al 1975, Chapman et al 1985). One type of rating scale is called *category judgment*, where subjects are given a structured categorized scale that represent pain intensity and asked to rate each stimulus on that scale (Chapman et al, 1985). A scale designed by Frank et al introduced a category rating scale that involved 8 cartoon faces with varied expressions, from laughter to total misery. The picture selection scores correlated well with responses made on a 5-point rating scale (Frank et al, 1982). The *visual analogue scale* (VAS) is another type of rating scale where subjects are told to indicate the intensity of pain by marking a 100 mm line that is labeled 'no pain' at one end and 'the worst pain possible' at the other (Joyce et al 1975). The patient will mark on the line where they perceive their pain, and then the pain intensity scores are calculated by measuring the distance from the left end point to the mark (Joyce et al 1975, Cohen et al 2008). Advantages to VAS include the ease of administration and understanding by the subjects, low cost, and ratio data (Cohen et al 2008).

The VAS is the gold standard for measuring pain in emergency medicine (Holdgate et al 2003). The Heft-Parker scale incorporates the patients common understanding of six pain descriptive words that are irregularly spaced on a 170mm horizontal line (Heft and Parker 1984). It is though that the patient will make category judgements on the basis of word meanings and that categorical rating are not merely an ordinal reading. Categorical scales are simply descriptive of the pain intensity on a four point scale from “no pain” to “severe pain”. Despite the simplicity of this scale, they have consistently been shown to be a reliable, comparable and reproducible measure for clinical pain trials (Averbuch and Katzper 2004).

RESULTS:

Few patients met the clinical criteria established for this study, with 29 patients enrolled (13 females and 16 males). Unfortunately, six patients failed to return their completed forms (5 males, and 1 female), providing data for 22 patients. Three pain measurement scales were used to analyze patient pain levels; VAS, HP and categorical. The Categorical scale was measured with 0 being no pain, 1 being mild pain, 2 being moderate pain, and finally 3 being severe pain. An example of the pain diary can be found in Appendix 3. All patients were seen between 2:00 and 4:00 PM during the graduate endodontic clinic emergency time. The three pain scales corresponded well with each other, and showed similar trends of each medication over the time periods.

The comparability between the four medication groups was analyzed according to patient characteristics such as age, gender, and presenting pain according to the VAS, Heft Parker and categorical reading. This is summarized in Table 1 below.

Gender	N	Mean Age	Mean Initial VAS (mm)	Mean Initial HP (mm)	Mean Initial Categorical
Males	16	40.69	60.05	104.3	2.3
Females	13	36.23	52.9	94.75	2.25
COMBINED	29	39.84	56.14	99.1	2.25

Table 1: Patient Baseline Characteristics based on gender

We then evaluated the comparability among the four medication groups for distribution of preoperative pulpal diagnosis (Table 2), apical diagnosis (Table 3), and tooth type (Table 4). The group with the initial dose of Ibuprofen followed by a second dose of Vicodin had more previously treated teeth compared to the other groups. The Naproxen group had no previously treated teeth in its' group. Ibuprofen and placebo groups also showed more cases with acute apical abscess compared with the other groups. Because our numbers were so low, this is one of the inevitable downfalls.

Medication Type	Total N	Necrotic	SIRP	Previously Treated
Placebo	6	2	3	1
Ibuprofen	4	1	2	1
Ibuprofen then Hydrocodone/ACA	6	0	3	3
Naproxen	6	4	2	0

Table 2: Distribution of pulpal diagnosis among the medication groups

Medication Type	Total N	Normal	SAP	AAA
Placebo	6	0	4	2
Ibuprofen	4	0	1	3
Ibuprofen then Hydrocodone/ACA	6	0	6	0
Naproxen	6	0	5	1

Table 3: Distribution of apical diagnosis among the medication groups

Medication Type	Total N	Anterior	Premolar	Molar
Placebo	6	2	0	4
Ibuprofen	4	1		3

Ibuprofen then Hydrocodone/ACA	6	0	0	6
Naproxen	6	0	0	6

Table 4: Distribution of tooth type among medication groups

We took readings of the patients perceived pain prior to initiation of root canal therapy, immediately after the first stage of root canal was carried out. The patients then took the pain diary home, and filled in the three pain scales at the following time intervals; 1 and 4 hours after taking dose #1 of medication, 1 hour after taking dose #2 of medication, then the following day at breakfast, lunch, dinner and bedtime.

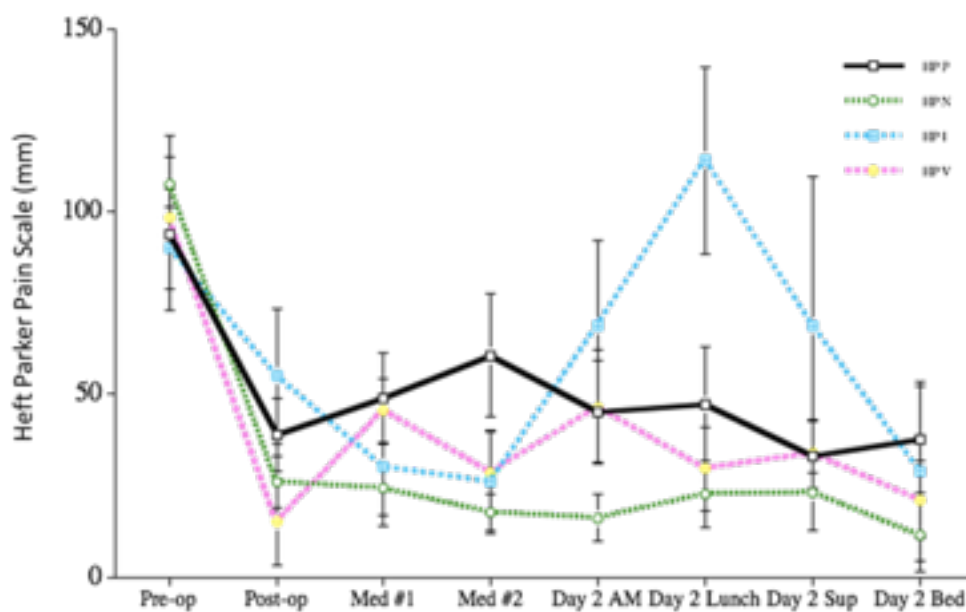


Figure 6: Graphical representation of Heft Parker readings at various time points for the various medication groups: Placebo (HP P), Naproxen (HP N), Ibuprofen (HP I), and Ibuprofen, followed by a dose of Vicodin (HP V). N=22 with Standard error bars shown

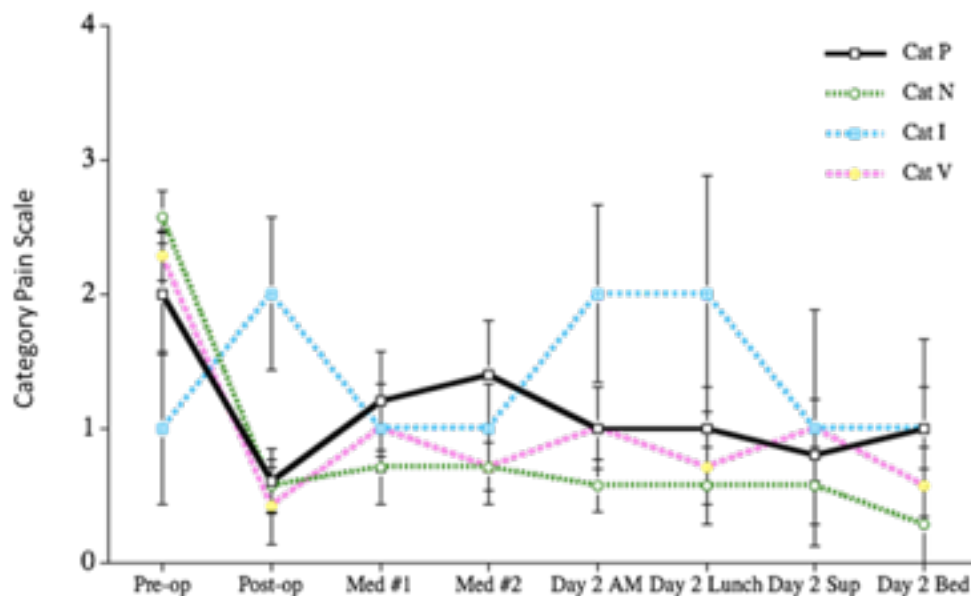


Figure 7: Graphical representation of categorical pain readings at various time points for the various medication groups: Placebo (CAT P), Naproxen (CAT N), Ibuprofen (CAT I), and Ibuprofen, followed by a dose of Vicodin (CAT V). N=22 with Standard error bars shown

	Initial-pain (mm)	Imm Post	1hr after dose #1	1hr after dose #2	Next day Break-fast	Next day Lunch	Next day Dinner	Next day Bed
Placebo	51.75	41.75	29.42	22.83	36.17	31.58	36.92	36.50
Naproxen	56.17	38.83	37.20	50.17	37.83	39.50	39.75	48.17
Ibuprofen	59.75	42.88	52.88	47.88	46.13	35.13	39.40	47.13
IBU +VIC	58.10	50.58	38.00	44.92	34.75	44.33	43.83	47.25

Table 5: The change in VAS reading at each time point based on medication. A higher number corresponds to a greater reduction in pain.

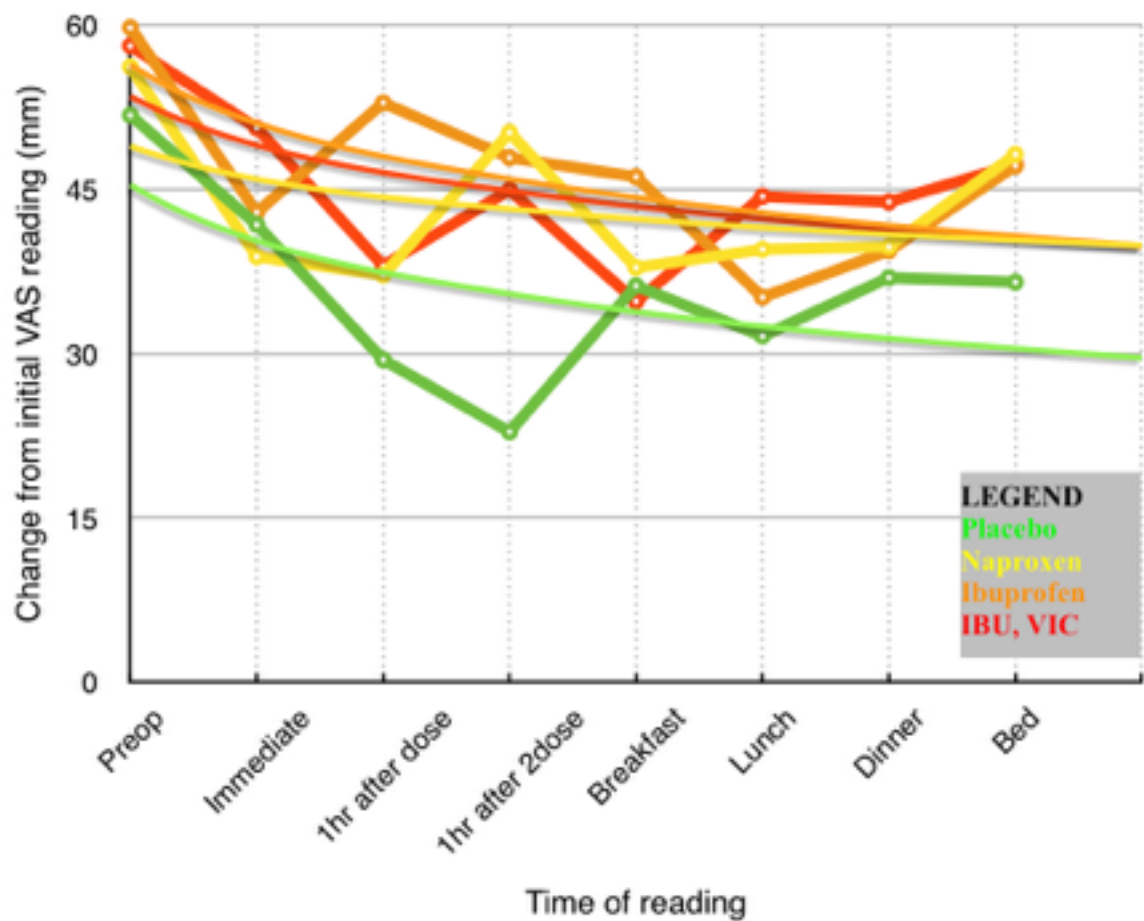


Figure 8: Graphical representation showing changes in VAS measurements (mm) at each time point for each medication. A logarithmic calculation is superimposed over the readings. Least reduction in pain noted in placebo group. All medication groups show similar reduction in pain at all-time points after the second dose

The VAS and HP showed the greatest reduction of pain immediately post op for all groups of medication except Ibuprofen (Figures 4 and 5). The placebo group showed an increase in pain an hour after its first dose, rebounding to a reading close to the preoperative pain

levels an hour after the second dose. However, the pain decreased the following day, increasing only slightly at the final reading “Day 2 bedtime”. The ibuprofen reached its lowest level of pain on the VAS and HP at one hour after the second dose of the medication. This group showed the highest level of rebound, to levels close to the preoperative pain according to the VAS scale, and even higher than the initial pain on the HP and categorical scales. The Ibuprofen and Vicodin group rebounded slightly one hour after taking the first dose from its minimum immediately post operatively, then decreased again one hour after the second dose. This group continued to decrease the following day, and did not see the same rebound as the Ibuprofen group. The Naproxen group had the lowest levels of pain on both the VAS and HP scales, decreasing further once the placebo pill was taken, roughly 7 hours after the Anaprox DS was taken. This trend continued the following day. The VAS scores were used to calculate the reduction in pain at each time point. This showed the least reduction in pain in the placebo group at all time intervals. Ibuprofen had the highest reduction in pain at the one hour following the first dose of medication mark. At all time intervals, the medicated groups were very similar (Table 5, and Figure 7).

Next, we analyzed if gender had any effect on postoperative pain and success of analgesic medication. Results can be found in figures 8, 9, 10 and 11 that follow:

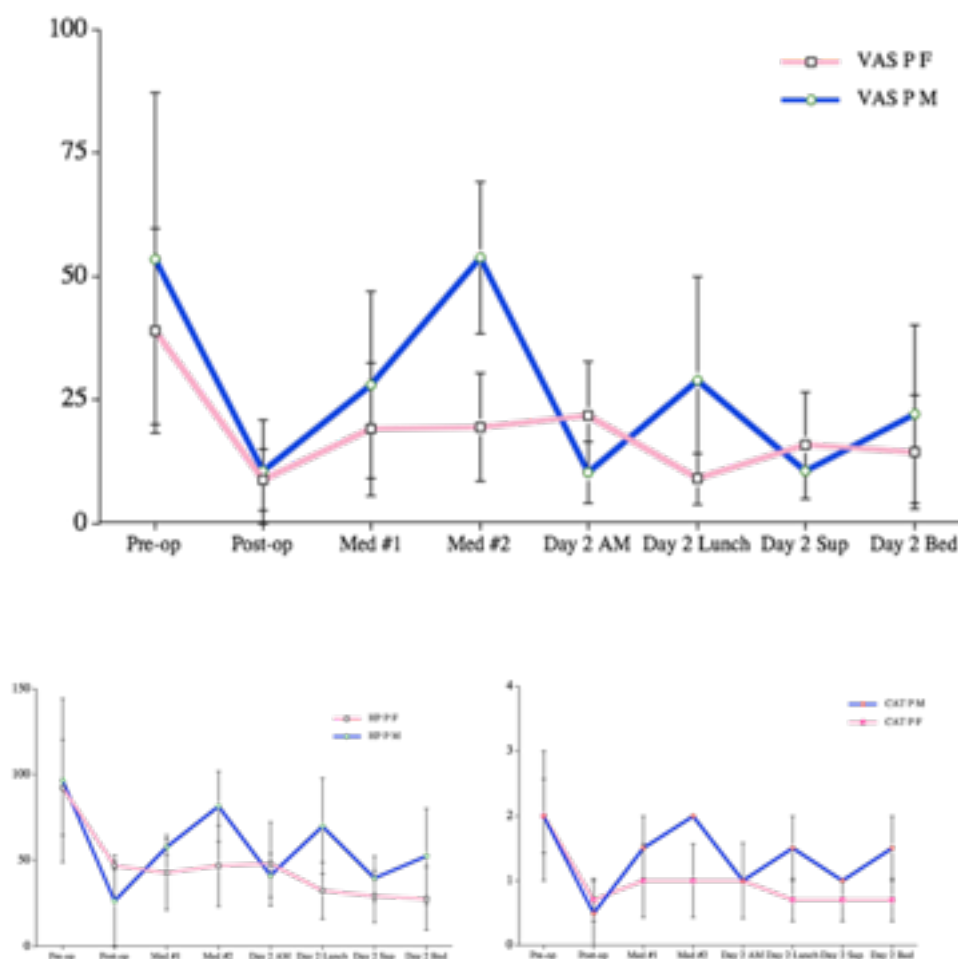


Figure 9: (From top clock-wise) VAS, categorical scale and HP pain readings at various time points for Placebo medication, where the blue line represents males and the pink, females. N=22 with Standard error bars shown

Figure 9 showed that males have a greater rebound in pain compared to females, with pain levels rebounding to preoperative lev-

els an hour after the second placebo dose was taken. The pain levels generally decreased the following day for both genders, however, the pain remained higher for the male group. Females showed better pain relief at later time intervals compared to men in both the HP and categorical scaled.

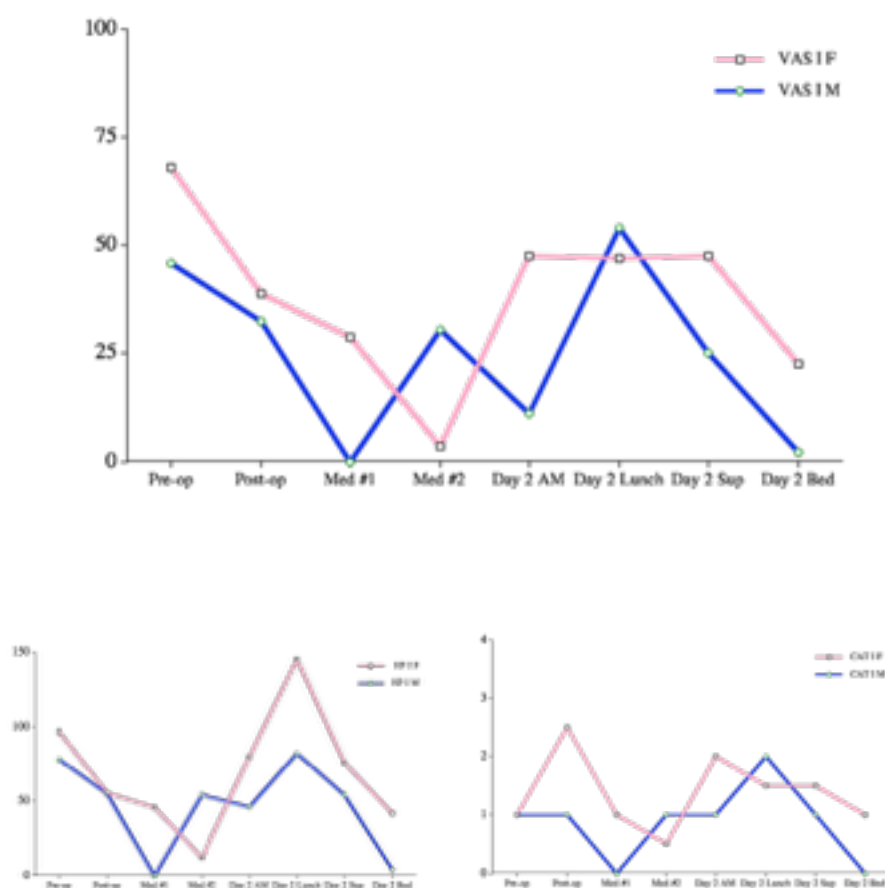


Figure 10: (From top clock-wise) VAS, categorical scale and HP pain readings at various time points for Ibuprofen medication, where the blue line represents males and the pink, females. N=22 with Standard error bars shown

Figure 10 showed that ibuprofen showed the lowest levels of pain for males one hour after the first dose was taken, and the lowest level of pain for females one hour after the second dose. Both males and females had a rebound of pain the following day to preoperative pain ranges. Males had better pain relief compared to females with this medication.

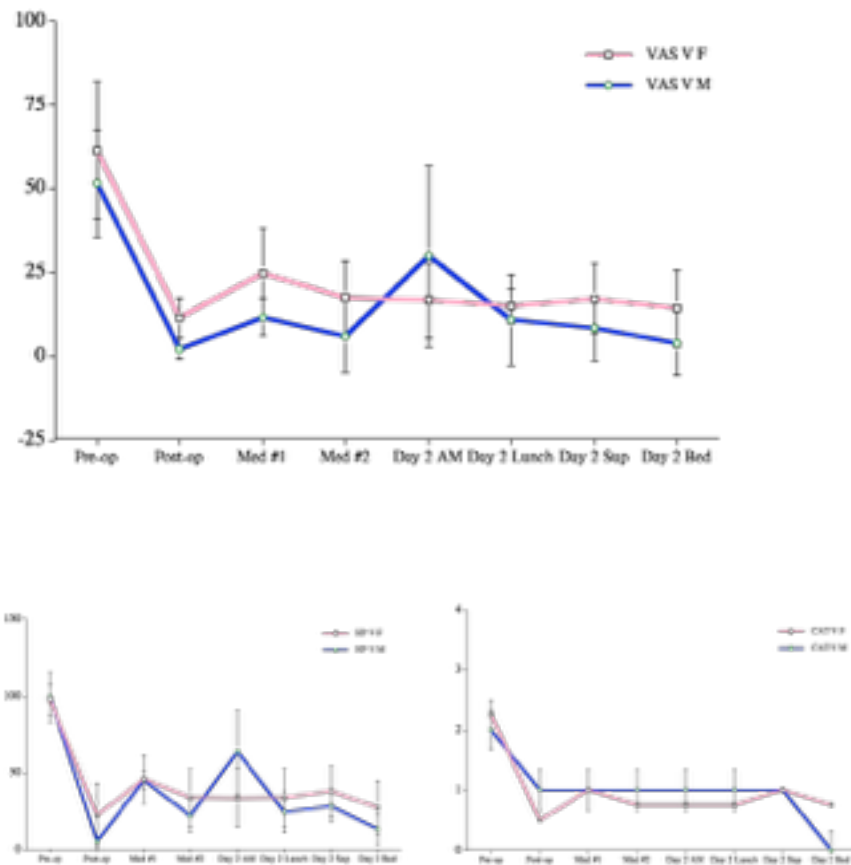


Figure 11: (From top clock-wise) VAS, categorical scale and HP pain readings at various time points for Vicodin and Ibuprofen medication, where the blue line represents males and the pink, females. N=22 with Standard error bars shown

Figure 11 above shows a similar decrease in pain levels for both the male and female groups once the ibuprofen and Vicodin combination were taken. There was a slight rebound in pain noted in the morning after for the male group, however, the pain levels decreased abruptly again, following a similar trend as the female group. Males had slightly more pain relief, especially at later time interval.

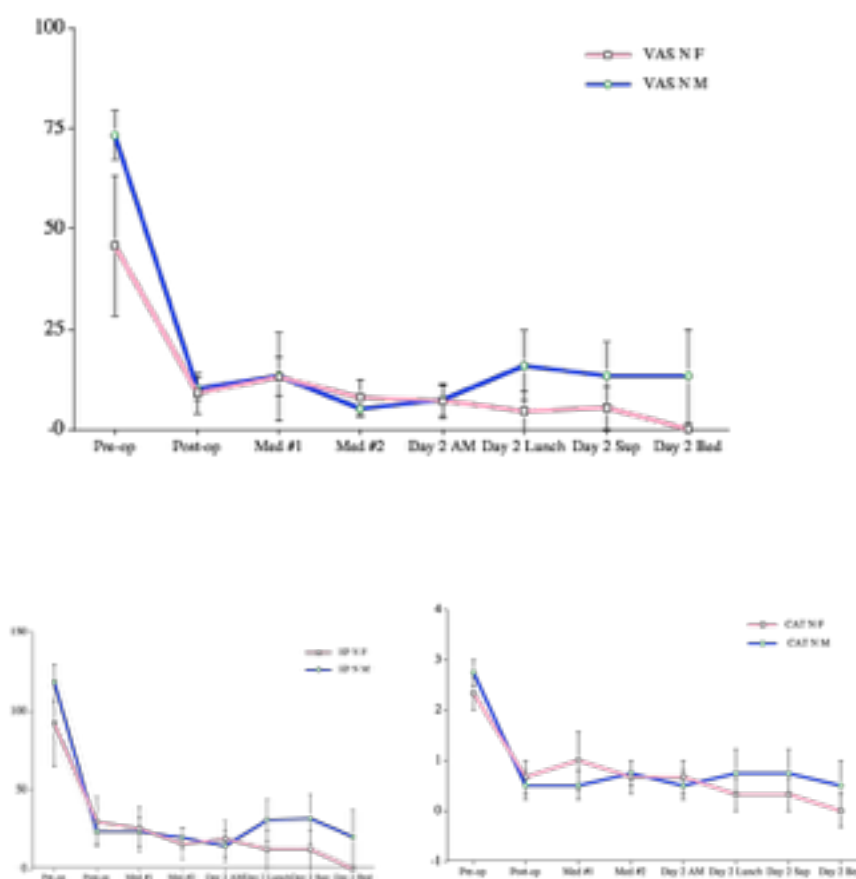


Figure 12: (From top clock-wise) VAS, categorical scale and HP pain readings at various time points for Naproxen medication, where the blue line represents males, and the pink females. N=22 with Standard error bars shown

Figure 12 shows a similar decrease in pain for both the male and female groups at all time intervals after the first dose of Anaprox was taken. This decrease in pain level continues for both male and females after the placebo dose was taken a few hours later. There was a slight rebound in pain noted the second day in the male group, while the female group continued to have decreased pain. Females had more relief at later time intervals for men in the Anaprox group. Finally, we analyzed whether or not the pulpal vitality played a role in post operative pain, and if this relationship was influenced by medication type.

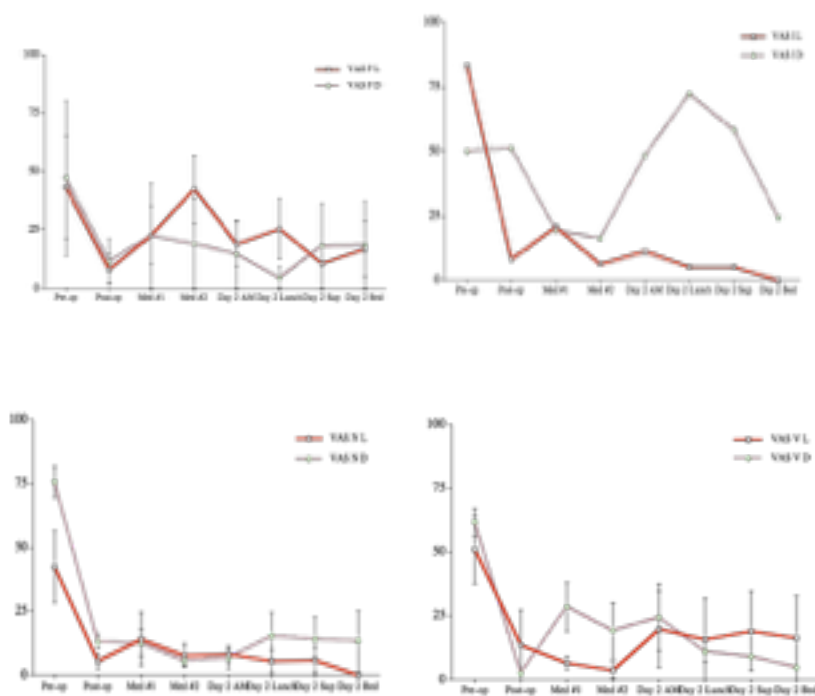


Figure 13: From top left clock wise; VAS scales of Placebo, Ibuprofen, Vicodin+Ibuprofen and Anaprox for vital pulps (L) and necrotic pulps (D). N=22 with Standard error bars shown

Figure 13 suggests that postoperative pain depends on pulp vitality. In the placebo group there was a similar decrease in pain intensity noted between both the vital and necrotic teeth. A slight rebound in pain postoperatively an hour after the second medication was taken was noted in the vital teeth compared to necrotic. In the Ibuprofen group, there was a sharp decrease in pain following postoperative treatment in the vital teeth, while the necrotic teeth showed quite a rebound of pain greater than the initial pain the following day. There was no such rebound noted in the Ibuprofen and Vicodin group, however, there was slightly more postoperative pain in the necrotic tooth during the first day after treatment. This pain decreased to a negligible level the following day in this group. Finally, the Naproxen group showed a sharp decline in pain postoperatively, which remained at low levels for the duration of the measurements. The necrotic group had slightly higher pain levels during the second day.

DISCUSSION:

Even when endodontic procedures are performed to the highest standard, the literature has shown that patients can suffer with postoperative pain up to 40% of the time, especially during the first 24 hours (Harrison et al 1983, Moskow et al 1984, Georgopoulou et al 1986, Oguntebi et al 1992, Liesinger et al 1993, Marshall and Liesinger 1993, Torabinejad et al 1994, Mattscheck et al 2001, Drenzo et al 2002). We had similar findings in our study. If one considers a 10mm or less reading on the VAS scale as mild pain, then about 63% were pain free at the 'lunch time' reading, (which roughly corresponds with 24 hours post operative) while 86% of our patient population were without pain at the final reading (about 36 hours post op). If one considers a reading between 30 mm and 50 mm moderate pain, then about about 14% of our patients had moderate pain at the 24 hour mark and about 23% at the 36 hour reading and. Finally, If one considers greater than a 50 mm reading on the VAS as severe pain, then 14% of the patients in our study had severe pain at the 'lunch time' reading and none at the final reading. The VAS readings corresponded well with the categorical scale.

The literature has also shown that pain is usually proportional to the severity of the inflammatory event which occurs in response to periradicular tissue trauma (Siqueira 2003). The best predictor of post-treatment endodontic pain is the severity of the pre-treatment pain (O'Keefe 1976, Harrison et al 1983, Marshall and Walton 1984, Torabinejad et al 1988, Mattscheck et al 2001). This was also found in our study, with patients presenting with the highest VAS preoperative pain having the highest post operative pain. Pharmaceutical aids in the way of analgesic agents or a combination of anti-inflammatory/analgesic agents can be used to control post-treatment pain. The type of pharmaceutical aid utilized has classically depended on the severity of the pain. NSAIDs such as ibuprofen have been shown to adequately manage mild to moderate dental pain (Cooper et al 1982, Mehlisch 2002). Moderate to severe pain is better managed with the addition of a narcotic agent such as hydrocodone to an NSAID (Hargreaves 1997, Dionne et al 1999).

The majority of the dental analgesic studies have been limited to the oral surgery model (Averbuch and Katzper 2000). Demographically, these studies tend to include a young, healthy, homogenous popu-

lation seeking elective surgery. These patients are usually free of acute or chronic inflammation prior to treatment (Mehlich 2002, Ryan et al 2008). In contrast, the endodontic model utilized in our study differs in that patients varied in age, health status, and preoperative pain presentation. The endodontic model also includes acute inflammatory states following treatment of chronic or acute inflammation (Ryan et al 2008). This mean there will likely be an accumulation of inflammatory cells and cell mediators such as bradykinin, histamine and oxidation products of arachidonic acid. All of these will lead to the synthesis of prostaglandins and other active substances, which will lead to hyperalgesia (Hargreaves et al 2001). The average age of patients who participated in our study was 39.84, with an average VAS and Heft-Parker readings of 56.14/100 and 99.1/170 respectfully (Table 1).

In this study, only 22 patients met the inclusion criteria and completed their at home pain diary. Participation in the study was limited to patients experiencing pre-treatment pain of 30mm or higher on the VAS, as they would be most likely to experience post treatment pain (O'Keef 1976). Among the other inclusion criteria mentioned in the material and methods section, the participating patients were not to have taken any form of analgesic four hours prior to their appointment.

This was the factor that proved to be the greatest barrier to getting participants, as the majority of the emergency patients had taken some form of analgesic prior to their appointment. All graduate endodontic emergency appointments offered at the University of Minnesota are in the afternoon, thus it is very likely that the patient would have taken some form of analgesic to get through the morning. Moreover, there were unfortunate time constraints that also limited the number of patients we could recruit. An increase in sample size would have definitely been more beneficial as it would have made the spread of pulpal and apical diagnosis and tooth time more evenly distributed (Tables 1-4). The original estimation of a statistically significant sample size was calculated to be around 120 patients.

Either 0.5% Bupivacaine (1:200000 epi) or 2% lidocaine (1:100000 epi) was given, and initial root canal therapy was carried out by a resident endodontist. There were four different operators used in an effort to increase the sample size and help recruit patients. All operators were residents and used the modified crown-down technique primarily with the use of rotary instrumentation. This is due to the fact that there would be less debris extruded apically and thus, and decreased chance of inflammatory response and postoperative pain (Ruiz-

Hubard et al 1987, Reddy and Hicks 1998). Sodium hypochlorite was used for irrigation as it is the most effective irrigant, and its use has been shown to decrease post operative pain when compared to saline (Harrison et al 1983). Calcium hydroxide was placed into a canal with a cannula to aid in the elimination of bacterial which may survive bio-mechanics instrumentation (Sjogren et al 1991). After the treatment was carried out, patients were administered one of the following regimen; 1) Placebo for both doses, 2) Anaprox DS (550mg Naproxyn sodium) 1st dose, Placebo 2nd dose; 3) Ibuprofen 800mg 1st dose, Ibuprofen 800 mg 2nd dose; and finally 4) Ibuprofen 800 mg + Vicodin (acetaminophen/hydrocodone) 1st dose, Ibuprofen 800 mg + Vicodin 2nd dose. These medications were taken when the patient got home after treatment, and then again at a 6-hour interval. Patients reported pain levels using categorical, VAS and Heft-Parker pain scales one hour after taking each dose of medication, and then the following day at breakfast, lunch, dinner and before bedtime.

There is evidence found in the literature to support the fact that administration of an analgesic drug will decrease post operative pain. Acetaminophen alone has been a useful medication that effectively lowers pain intensity in most patients, with the advantage that it it does

not irritate the stomach and intestinal lining (Guggenheimer and Moore 2011, Kraglund 2014). Acetaminophen acts by inhibiting prostaglandin synthesis in the CNS and by interacting with serotonin and nitric oxide mechanisms (Bjorkman 1995). It is able to cross the blood-brain barrier which will allow inhibition of central hyperalgesia produced by neurotransmitters such as substance P (Bjorkman 1995, Aminoshariae and Khan 2011). Acetaminophen, however, has a narrower window of safety compared with NSAIDs. Its byproduct NAPQI may accumulate in the liver resulting in hepatic damage (Forrest JA et al 1982, FDA drug safety communication 2014). Because of differing mechanisms and sites of action, acetaminophen can be used in combination with either an NSAID or an opioid such as hydrocodone to increase its analgesic effect, as well as decrease the dose of Acetaminophen needed (Kraglund 2014, Menhinick et al 2004, Guggenheimer and Moore 2011).

Narcotic analgesics are a class of analgesics that are useful in treating moderate to severe pain not alleviated by NSAIDs or acetaminophen. Hydrocodone was utilized in this study and is a semi-synthetic opioids with multiple actions qualitatively similar to those of morphine. Its mechanism of action is that it will bind and activate the

mu (μ) opiate receptor in the CNS, as does the endogenous opiate beta-endorphin (Hargreaves et al 1987). These actions inhibit neurotransmitter (e.g., SP) release and/or hyper-polarize cell membranes, thus inhibiting neuronal activity (Law et al 2000). Vicodin which consists of 325 mg of Acetaminophen and 7.5 mg Hydrocodone was taken with 800mg Ibuprofen. This study used the NSAIDs Ibuprofen and Naproxen. These drugs inhibit prostaglandin synthesis by decreasing the activity of cyclo-oxygenase enzyme (COX), which is released with tissue injury and detected in high concentrations in macrophages, monocytes, leukocytes in response to mediators of inflammation (Cooper et al 1993, Arslan et al 2011). This class of drug is associated with a dose-dependent risks, such as the development of serious gastrointestinal bleeding (Vane and Botting 1998). Ibuprofen, which is one of the most commonly used NSAID (Menhinick et al 2004, Cooper et al 1993) and was utilized in our study at two high doses of 800 mg each. Anaprox DS (550 mg Naproxen) has improved absorption characteristics, and longer plasma levels compared to Ibuprofen (Young et al 2013). This drug has the benefit of needing fewer doses which carries fewer risks long term.

There were no untoward events through the study, and no patients required additional analgesic intervention. In the literature, the incidence of complications due to NSAIDs is between 1.1 to 2.4 %, with the majority of issues being gastric bleeding (Michels et al 2012). All patients participating in this study showed a decrease in pain level immediately following initial root canal therapy. The pain level rose again in all groups at the next time point which one would expect as this would correspond with the local anaesthetic wearing off (Malamed 1990). Again, there were two types of local anaesthetic used in our study, thus this should be considered when analyzing the data. It has been shown that long acting anaesthesia such as 0.5% bupivacaine will have a significant decrease in postoperative pain compared with 2% lidocaine (Dionne et al 1999, Moore and Dunsky 1983). The effects of these local anaesthetics were looked at in another study.

The placebo group showed a significant decrease in pain when comparing the initial pain levels, which suggests that definitive treatment will decrease the pain intensity. This finding is consistent with the literature (Doroschak et al 1999, Menhinick et al 2004). The placebo effect is another possibility for this finding. A greater decrease in postoperative pain was seen in the medication groups when

compared to the placebo group at later time periods with the exception for Ibuprofen (Figures 4, 5, 6). The Ibuprofen group had its lowest levels of pain one hour after the medication was given, however, there was a rebound in pain to levels near the initial pain during the second day, with a maximum reading of pain occurring at lunch time. Studies have shown that taking a single dose of oral ibuprofen can augment concentrations of circulating pro inflammatory cytokines, such as TNF, IL1 and elastases (Pinas et al 1991). Using stimulated peripheral blood mononuclear cells, Endres et al also found an increase in TNF, IL1 alpha and beta synthesis in subjects who had taken Ibuprofen. There were parallel increases in PGE2 also observed in this group. The conclusion was made that there is a 'rebound' increase in cytokine-induced cytokine synthesis in groups that had taken 200mg of Ibuprofen for 2 weeks, at 12 days after discontinuing this dose (Endres et al 1996). This is a plausible cause of the rebound in pain after the high 1600 mg dose taken the day prior. Patients were also likely taking Ibuprofen in the days leading up to the dental appointment.

The rebound in pain was not noted in the 800 mg Ibuprofen and Vicodin group (Figures 4, 5, 6). Vicodin is composed of 7.5 mg of Hydrocodone and 325mg Acetaminophen, and has the benefit of com-

binning the μ -agonist of the opioids with the central and peripheral inhibition of PGE₂ of the Acetaminophen. These components work via different mechanisms proving beneficial in the management of pain. Menhenecks study showed that a combination of ibuprofen and acetaminophen had superior analgesia at 8 hours post operatively compared to ibuprofen alone and or placebo (Menhenick et al 2004). The literature has shown the addition of a small amount of opioids to NSAIDs can be quite beneficial, especially with moderate to severe pain (Dionne et al 2001, Litouwski et al 2005). When prescribing these combination drugs such as Vicodin, it is important that the clinician plays particular attention to the amount of acetaminophen used, and that the maximum daily dose of 3 g is not exceeded due to dangers of liver damage (Guggenheimer 2012, Aminoshair and Khan 2015).

The naproxen group showed the greatest reduction in pain compared to all other groups at every time point after the medication was taken. The initial pain levels were similar when comparing to the other groups (Figure 4, 5, 6). Doses between 200 and 400 mg have shown to be effective for analgesia over a 12 hour time period in the literature (Young et al 2013, Li-Wan-Po et al 2013). These findings are expected when you consider the pharmacodynamics of these medications.

Ibuprofen will reach its maximum plasma concentration between 0.5 to 3 hours with an elimination half life between 2 to 3 hours, while Naproxen's maximum plasma concentration is reached between 1-3 hours, with an elimination half life between 12 to 17 hours (drugs.com). Anaprox DS has enteric-coating that is designed to protect your stomach, and offer extended release of medicine.

Males and females had similar post operative pain. When analyzing the results of the placebo group (Figure 8), it is noted that the male group had a rebound in pain similar to the preoperative pain one hour after the second dose of placebo was given. The following day showed a continuation of slightly elevated postoperative pain compared to females. This contradicts the literature which concludes that female gender is normally a red flag for the possibility of post operative flare-ups (Torabinejad et al 1988, Ng et al 2004, Polycarpou et al 2005). Other literature that found gender has no effect on the prevalence of post operative pain suggested that those studies that did were biased as females were more likely to seek treatment even for mild pain (Locker and Grushka 1987, MacEntee et al 1993). Among the patients taking 800mg Ibuprofen, both Males and females showed a dramatic rebound in pain on day two. This rebound was more dramat-

ic on the HP scale for females (Figure 9). There were similar pain scale readings between the two genders for both the Ibuprofen and Vicodin group and Naproxen groups (Figures 10 and 11). There was greater pain relief in the later time intervals among females in the Naproxen group compared to males, which would correspond with what the literature (Kshirsagar et al 2008, Ryan et al 2008).

Studies have been contradicting when considering preoperative tooth vitality as a factor, with some suggesting there is greater discomfort in necrotic teeth (Walton and Fouad 1992) and others suggesting that pulpal diagnosis has no significance, especially if apical patency is maintained (Arias et al 2009, Arias et al 2013). The results obtained in this study were equally confounding, and varied between the placebo group and the Ibuprofen group. In the placebo group there was a similar initial decrease in pain intensity noted between both the irreversible pulpitis (IRP) and necrotic teeth however there was more of a rebound postoperatively in the IRP teeth compared to necrotic (Figure 13). This could be due to the up to 8-fold increase substance P levels in IRP tissues (Bowles et al. 2003). Prostaglandin are also present in higher concentrations in acutely inflamed teeth, thus increasing inflammation and discomfort (McNicholas et al. 1991). Mechanical allodynia is

more common in teeth diagnosed as IRP compared to necrotic teeth (67 vs 56% respectively) and can add to the post operative discomfort felt by the patient (Olgart et al 1989). In the Ibuprofen group, there was a sharp decrease in pain following postoperative treatment in the IRP teeth, while the necrotic teeth showed quite a rebound of pain greater than the initial pain the following day. Perhaps this could be due to the rebound effect that can be seen with Ibuprofen discussed by Endres et al in 1996 and mentioned previously. With necrotic teeth, there will likely be an accumulation of inflammatory cells, bradykinin, histamine and oxidation products of arachidonic acid due to the chronic nature of the disease. These will lead to the synthesis of prostaglandins and other active substances, which will lead to hyperalgesia (Hargreaves et al 2001). These chronic inflammatory products as well as bacteria can be extruded after instrumentation, thus leading to more post-operative pain (Seltzer and Naidorf 1985, Torabinejad et al 1988, Siqueira et al 2004). There was only negligible differences between the IRP and necrotic teeth in the Ibuprofen and Vicodin and Naproxen groups, both showing a sharp decline in pain postoperatively and remaining at low levels for the duration of the measurements.

Categorical, VAS and Heft-Parker scales were filled in by the patients to indicate the pain felt at certain time intervals. The quantification of subject responses on categorical scales can be problematic as the categorization does imply rank ordering. The category boundaries are not known and the approximation of the ranked categories to equal intervals is often assumed rather than demonstrated (Chapman et al 1985). Moreover, numbers were assigned to categories in order to analyze the data. This is questionable unless the investigator has evidence that the subjects treat the categories like equally spaced numbers (Joyce et al 1975, Chapman et al 1985). Heft Parker categories are not equally spaced, and these irregular spaces reflect differences in the meaning of the descriptors used on the scale. VAS tend to be preferable for clinical applications, as categorical scales may produce artificially augmented scores (Joyce et al 1975). One issue with this scale, however, is that we are assuming that pain is a unidirectional experience which varies only in intensity. Thus, these scales are liable to response biases. Broad ranges of psychological experiences are compressed onto artificially small continuums. Subjects will tend to spread responses over the entire scale regardless of magnitude of actual sensations (Chapman et al 1985).

Further recruitment of patients using this model and analgesic combinations would be beneficial for the treatment and or prevention of post operative discomfort following endodontic treatment. A suggested change would be to recruit and treat patients in the morning, when they are less likely to have taken an analgesic.

Conclusion

The outcome of this study suggests that primary endodontic treatment will greatly decrease the pain felt by the patient. It is suggested from this study that high doses of Ibuprofen followed by abrupt stop can lead to a rebound in pain. Anaprox DS shows a consistently lower pain score at longer time periods, with this being more marked for females. There was not much difference in post operative pain scores between men and women. Tooth Vitality did not effect post operative pain. Due to low numbers of participants, the null hypothesis that there will be no difference between the various groups of analgesics for post operative pain control can not be either accepted or rejected. More research using this model and analgesic combinations would be useful as the administration of definitive dental treatment with an appropriate analgesic or analgesic combination is important for the management of the patient with endodontic pain

Bibliography

Ahlquist M, Franzen O, Edwall L, Fors U, Haegerstam G., Quality of pain sensations following local application of allogenic agent on the exposed human tooth pulp: A psychophysical and electrophysiological study. In Fields H (ed) *Advances in pain research and therapy*, vol 9. New York: Raven Press, 1985; 351-359

Aminoshariae A, Khan A. Acetaminophen: Old Drug, new issues. *J ended* 2015; 41: 588-593

Anderson R, Thomas DW. "Toothache stories" a qualitative investigation of why and how people seek emergency dental care. *Community Dent Health* 2003; 20: 106-11

Arias A, Azabal M, Hidalgo J, Macorra J. Relationship between post-endodontic pain, tooth diagnostic factors and apical patency. *Int Endod J* 2009; 35(2) 189-192

Arias A, de la Macorra JC, Hidalgo JJ, Azabal M. Predictive models of pain following root canal treatment: A prospective clinical study. *Int Endod J* 2013; 46(8):784-93

Arslan, H, Topcuoglu HS, Aladag H. Effectiveness of tenoxicam and ibuprofen for pain prevention following endodontic therapy in comparison to placebo: a randomized double-blind clinical trial. 2011. *Journal of oral science* :53(2):157-61

Averbuch M, Katzper M. Assessment of visual analog versus categorical scale for measurement of osteoarthritis pain. *J Clin Pharmacy* 2004; 44(4): 368-72

Barden J, Edwards J, Moore A, McQuay H. Single dose oral paracetamol for postoperative pain. *Cochrane database Syst Rev* 2004;(1) Accessed March 10th, 2015

Bacsik CJ, Swift JQ, Hargreaves KM. Toxic systemic reaction of bupivacaine and etidocaine. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995;79:18-23

Beaver WT, Forbes JA, Barkoszi BA, Ragland RN, Hankle JJ. An evaluation of ibuprofen and acetaminophen in postoperative oral surgery pain. *Clin Pharmacol Ther* 1987; 41:180

Becker D, Reed K. Essentials of local anaesthetic pharmacology. 2006. *Ants Prog.* 53(3): 98-109

Becker RC. COX-2 Inhibitors. *Tex Heart Inst J.* 2005; 32(3):380-383

Bergenholtz G, Lindhe J. Effect of soluble plaque factors on inflammatory reactions in the dental pulp. *Stand J Dent Res* 1975;3:418-423

Bjorkman R, Hellman KM, Hedner J, Hedner T, Henning M. Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. *Pain* 1994; 57: 259-264

Bowles WR, Withrow JC, Lepinski AM, Hargreaves KM. Tissue levels of immunoreactive substance P are increased in patients with irreversible pulpitis. *J Endod* 2003 Apr;29(4):265-7

Byres MR. Development of sensory innervation in dentine. *J Comp Neural* 1980; 191: 413-427

Byres MR. Dental sensory receptors. *Int Rev Neurobiol* 1984; 25:39-94

Byers MR, Narhi MV. Dental injury models: Experimental tools for understanding neuroinflammatory nociceptor functions. *Crit Rev Oral biol* 1999; 10: 4-39

Byers MR, Narhi MVO. Nerve supply of the pulpodentin complex and responses to injury. In: Hargreaves KM, Goodis HE, eds. *Seltzer and Bender's dental pulp*. 4th ed. Chicago: Quintessence Publishing Co, Inc, 2002:151-79

Chapman CR, Casey KL, Dubner R, Foley KM, Gracely RH, Reading AR. Pain measurement: an overview. *Pain* 1985 22: 1-31

Chiang C, Park S, Kwan C, Hu J, Sessle BJ. NMDA receptor mechanisms contribute to neuroplasticity induced in caudalis nociceptive neurons by tooth pulp stimulation. *J Neurophysiol* 1998; 80:2621-2631

Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat Neurosci.* 2012 Jul 26; 15(8):1063-7

Clissold SP. Aspiring and related derivatives of salicylic acid. *Drugs* 1986. 32 (Suppl 4) 8-26

Cohen L, Lemanek K, Blount R, Dahlquist L, Lim C, Palermo T, McKenna K, Weiss K. Evidence-based assessment of paediatric pain. *J Pediatr psychol.* 2008 Oct; 33(9): 939-955

Cooper SA, Quinn PD, MacAfee K, Hersh EV, Sullivan D, Lamp C. Ibuprofen controlled-release formulation. A clinical trial in dental impaction pain *Oral surgery.* 1993 *Oral Medicine and Oral pathology*; 75: 677-83

Creech JL, Walton RE, Kaltenbach R. Effect of occlusal relief on endodontic pain. *J Am Dent Assoc.* 1984; 109(1): 64-7

Dani M, Guindon J, Lambert C, Beulieu P. The local antinociceptive effects of paracetamol in neuropathic pain are mediated by cannabinoid receptors. *Eur J Pharmacy* 2007; 573:214-5

Diogenes A, Ferraz CC, Akopian AN, Henry MA, Hargreaves KM. LPS sensitises TRPV1 via activation of TLR4 in trigeminal sensory neurons. *J Dent Res* 2011; 90:759-764

DiRenzo A, Gresla T, Johnson BR, Rogers M, Tucker D, BeGole EA. Postoperative pain after 1- and 2- visit root canal therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2002. 93(5): 605-10

Drugs.com: Naproxen: <http://www.drugs.com/dosage/naproxen.html>. Accessed July 10th, 2015

Dubner R, Bennet GJ. Spinal and trigeminal mechanisms of nociception. Annual reviews in Neuroscience 1983;6:381-418

Duncan R, Gilbert G, Peek, C, Heft M. The dynamics of toothache pain and dental services utilization: 24-month incidence. Journal of Public Health Dentistry 2003; 63; 227-234.

Endres S, Whitaker RED, Ghorbani R, Meydani N, Dinarello CA. Oral aspirin and ibuprofen increase cytokine-induced synthesis of IL1B and of tumour necrosis factor alpha ex vivo. Immunology, 1996;87:264-270

FDA drug safety communication: Prescription acetaminophen products to be limited to 325mg per dosage unit; boxed warning will highlight potential for severe liver failure. <http://www.fda.gov/Drugs?DrugSafety/ucm239821.htm>. Accessed March 13th, 2015.

FDA drug safety communications: Non-prescription use of ibuprofen and the risks of gastrointestinal and renal toxicity. http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882B2_06_International%20Ibuprofen%20Foundation.htm. Accessed June 29th, 2015.

Ferraz CC, Henry MA, Hargreaves KM, Diogenes A. Lipopolysaccharide from Porphyromonas gingivalis sensitizes capsaicin-sensitive nociceptors. J Endod 2011; 37:45-48

Forrest JA, Clements J, Prescorr L. Clinical pharmacokinetics of paracetamol. Clin Pharmacokinet 1982; 7:93-107.

Frank AJM, Moll JMH, Hort JF. A comparison of three years of measuring pain. Rheumatoid. Rehab. 21(1982) 211-217

Gatoulis SC, Voelker M, Fisher M. Assessment of the efficacy and safety profiles of aspirin and acetaminophen with codeine: Results from 2 randomised, controlled trials in individuals with tension-type headaches and postoperative dental pain. Clin Ther 2012; 34(1): 138-48

Genet JM, Hart AA, Wesselink PR, Thoden van Velzen SK. Preoperative and operative factors associated with pain after the first endodontic visit. *Int Endod J*, 1987. 20(2): 53-64

Gilbert GH, Shelton BJ, Chavers LS, Bradford EH. The paradox of dental need in a population-based study of dentate adults. *Med Care* 2003; 41: 119-134

Goodis H, Bowles W, Hargreaves KM. Prostaglandin E2 enhances bradykinin-evoked iCGRP release in bovine dental pulp. *J Dent Res* 2000; 79: 1604-1607

Georgopoulou M, Anastassiadis P, Sykaras S. Pain after chemomechanical preparation. *Int Endod J*. 1986; 19: 309-314

Guggenheimer J, Moore PA. The therapeutic applications of and risks associated with acetaminophen use: A review and update. *J Am Dent Assoc* 2011; 142:38-44

Hargreaves KM, Dionne R, Goldstein D, Mueller G, Dubner R. Naloxone, fentanyl and diazepam modify plasma beta-endorphin levels during surgery. *Clin Pharmacol Ther* 1986; 40:165-171

Hargreaves KM, Swift JQ, Roszkowski MT, Bowles W, Garry MG, Jackson DL. Pharmacology of peripheral neuropeptide and inflammatory mediator release. *Oral Surg Oral Med Oral Pathol* 1994;78:503-10

Hargreaves KM, Milam S. Mechanisms of pain and analgesia. In: Dionne R, Phero J. *Management of pain and anxiety in dental practice*. New York; Elsevier, 2001 : 18-40

Hargreaves KM. Peripheral mechanisms of inflammatory pain, in Sessle B, Dubner R, Lavigne G. *Orofacial Pain: from basic science to clinical management*. Chicago: Quintessence, 2001: 59-66

Hargreaves KM, Goodis HE, eds. *Seltzer and Bender's dental pulp*. 4th ed. Chicago: Quintessence Publishing Co, Inc, 2002:151-79

Hargreaves KM, Hutter JW, Endodontic pharmacology. In: Cohen S, Burns R (eds) *Pathways of the pulp* ed 8, St Louis: Mosby, 2002: 665-685

Harrison JW, Baumgartner JC, Svec TA. Incidence of pain associated with clinical factors during and after root canal therapy. Part 1. Interappointment pain. *J Endod*, 1983 9(9): 384-87

Harrison JW, Baumgartner JC, Svec TA. Incidence of pain associated with clinical factors during and after root canal therapy. Part 2. Postobturation pain. *J Endod*, 1983 9(10): 434-38

Hasler JF, Mitchel DF. Analysis of 1628 cases of odontalgia; a corroborative study. *J Indianap Dist Dent Soc* 17:23 1963

Hashioka K, Yamasaki M, Nakane A, Horiba N, Nakamura H. the relationship between clinical symptoms and anaerobic bacteria from infected root canals. *J Endod* 1992; 18: 558-561

Hasselgren G, Reit C. Emergency pulpotomy: Pain relieving effect with and without the use of sedative dressings. *J Endod* 1998; 15(6): 254-6

Heft MW, Parker SR. An experimental basis for revising the graphic rating scale for pain. *Pain* 1984; 19(2): 153-61

Henry MA, Hargreaves KM. Peripheral mechanisms of odontogenic pain. *Dent Clin N Am* 2007;51:9-44

Hohmann AG, Herkenham M. Cannabinoid receptors undergo axonal flow in sensory nerves. *Neuroscience* 1999; 92: 1171-1175

Holdgate A, Asha S, Craif J, Thompson J. Comparison of a verbal numeric rating scale with the visual analogue scale for the measurement of acute pain. *Emerg Med (Fremantle)* 2003; 15(5-6):441-6

Holstein A, Hargreaves KM, Niederman R. Evaluation of NSAIDs for treating post-endodontic pain. *Endo Topics* 2002;3:3-13

Huber M, Terezhalmy G. The use of COX-2 inhibitors for acute dental pain. *J Am Dent Assoc* 2006; 137:480-7

Huskisson E. Measurement of pain. *The Lancet* 1974; 204:7889: 1127-1131

Itoh K. The distribution of nerves in human deciduous and permanent teeth. *Arch Histolog Jap* 1976;39:379-99

Jiang HW, Zhang W, Ren BP, Zeng JF, Ling JQ. Expression of toll like receptor 4 in normal human odontoblast and dental pulp tissue. *J Endod* 2006; 32: 747-51

Johnsen DC, Harshbarger J, Rymer HD. Quantitative assessment of neural development in human premolars. *Anat Rec* 1983: 205; 421-9

Johnsen DC. Innervation of teeth: qualitative, quantitative, and developmental assessment. *J Dent Res* 1985;64 (Special Issue):555-63.

Jostes JL, Holland GR. The effect of occlusal reduction after canal preparation on patient comfort. *J Endod.* 1984; 10(1): 34-7

Joyce CR, Zutish DW, Hrubes V, Mason RM. Comparison of fixed interval and visual analogue scales for rating chronic pain. *Europ. J. Clin. Pharmacol.* 1975 8:415-420

Kakehashi S, Stanley HR, Fitzgerald RJ. The effects of surgical exposures of dental pulps in germfree and conventional laboratory rats. *J South Calif State Dent Assoc* 1966;34:449-51

Katz J, Melzack R Measurement of pain. *Surgical clinics of north america* 1999;79: 231-52

Keiser K, Byrner BE. Endodontic pharmacology. in: Hargraves KM, Cohen S *Pathways of the pulp*, ed 10. St Louis: Mosby, 2011: 671-690

Khabbaz MF, Anastasiadis PL, Sykaras SN. Determination of endotoxins in the vital pulp of human carious teeth: Association with plural pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 91: 587 - 593

Kopp E, Ghosh S. Inhibition of NF-kappa B by sodium salicylate and aspirin. *Science*, 1994. 265(5174): 956-9

Kraglund F. Acetaminophen plus a nonsteroidal anti-inflammatory decreases acute postoperative pain more than either drug alone. *JADA*, 2014; 145(9):966-968

Kshirsagar S, Gear R, Levine J, Verotta D. A mechanistic model for the sex-specific response to nalbuphine and naloxone in postoperative pain. *J Pharm Pharmacol* 2008;35:69-83

Law PY, Wong YH, Loh HH. Molecular mechanisms and regulation of opioid receptor signaling. *Annu Rev Pharmacol Toxicol*. 2000; 40: 389-430

Lee YS, Kim H, Brahim JS Acetaminophen selectively suppresses peripheral prostaglandin E2 release and increases COX-2 gene expression in a clinical model of acute inflammation. *Pain* 2007; 129: 279-86

Lipton J A, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. *J Am Dent Assoc* 1993;124:115-21

Liesinger A, Marshall FJ, Marshall JG. Effect of variable doses of dexamethasone on post treatment endodontic pain. *J Endod*, 1993. 19(1): 35-9

Li-Wan-Po A, Chen S, Petersen B, Want Y. No need for rescue medication (NNR) as an easily interpretable efficacy outcome measure in analgesic trials: Validation in an individual patient meta-analysis of dental pain placebo-controlled trials of naproxen. *J Clin Pharm Ther* 2013; 38:36-40

Locker D, Grushka M. Prevalence of oral and facial pain and discomfort: preliminary results of a mail survey. *Community Dent Oral Epidemiol* 1987; 15:169-72.

MacEntee MI, Stolar E, Glick N. Influence of age and gender on oral health and related behaviour in an independent elderly population. *Comm Dent and Oral Epi* 1993;21; 234-39

Madison S, Whitsel EA, Suarez-Roca H, Maixner W. Sensitizing effects of leukotriene B4 on intradental primary afferents. *Pain*, 1992. 49(1): 99-104

Malamed SF. *The handbook of Local Anesthesia*. 3rd ed. Mosby, St. Louis. 1990.

Malamed SF, Reed KL, Fonner AM. Local Anesthesia Part 2; Technical considerations. *Anesth Prog*. 2012; 59(3): 127-137

Marshall J, Walton R, The effect of intramuscular injection of steroid on post treatment endodontic pain. *J Endod* 1984; 10: 115-131

Marshall J, Liesinger A. factors associated with endodontic post treatment pain. *J Endod* 1993; 19: 573-575

Mattscheck DJ, Law AS, Noblett WC. Retreatment versus initial root canal treatment: Factors affecting posttreatment pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001. 92(3) 321-4

McGilveray I, Mattock G. Some factors affecting the absorption of paracetamol. *J Pharm Pharmacy* 1972; 24:615-9

McNicholas S, Torabinejad M, Blankenship J, Bakland L. The concentration of prostaglandin E2 in human periradicular tissues. *J of endod*. 1991;17:97-100

McQuay HJ, Carroll D, Watts PG, Juniper RP, Moore RA. Codeine 20mg increases pain relief from ibuprofen 400mg after third molar surgery. A repeat-dosing comparison of ibuprofen and an ibuprofen-codeine combination. *Pain* 1989; 37: 7-13

Mehlisch DR. The efficacy of combination analgesic therapy in relieving dental pain. *J Am Dent Assoc* 2002; 133(7):861-71

Mehrvarzfar P, Abbott V, Saghiri A, Delvarani A, Asgar K, Lotfi M, Karamifar K, Kharazifard MJ, Khabazi H. Effects of three oral analgesics on postoperative pain following root canal preparation: a controlled clinical trial. *Int endod J* 2012;45: 76-82

Menhinick, KA, Gutman JL, Regan JD, Taylor SE, Buschang PH. The efficacy of pain control following nonsurgical root canal treatment using ibuprofen or a combination of ibuprofen and acetaminophen in a randomised, double-blind, placebo-controlled study. *Int Endod J* 2004;37(8):531-41

Millan MJ. Descending control of pain. *Prog Neurobiol* 2002: 66: 355-474

Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute poroperative pain in adults. *Cochrane Database Syst Rev* 2011: Sep 7(9)

Michels SL, Collins J, Reynolds MW, Abramsky S, Paredes_diaz A, McCarberg B. Over-the-counter ibuprofen and risk of gastrointestinal bleeding complications. A systematic literature review. *Curt Med Res Opin.* 2012; 28(1):89-99

Morse DR, Furst ML, Koren LZ, Bolanos OR, Esposito JV, Yesilsoy C. Comparison on diflunial and an aspirin-codeine combination in the management of patient having one visit endodontic therapy. *Cline Ther* 1987; 9(5): 500-11

Moore JL, Dunskey PA. Bupivacaine anesthesia – a clinical trial for endodontic therapy. *Oral Surg Oral Med Oral Pathol* 1983;55:176-9

Moore RA, Straube S, Paine J, Derry S, McQuay H. Minimum efficacy criteria for comparisons between treatments using individual patient meta-analysis of acute pain trials: examples of etoricoxib, paracetamol, ibuprofen, and ibuprofen/paracetamol combinations after third molar extraction. *Pain* 2011;152:982–9

Moos HL, Bramwell JD, Roahen JO. A comparison of pulpectomy alone versus pulpectomy with trephination for relief of pain. *J Endod* 1996; 22(8): 422-5

Nair PNR. Neural elements in dental pulp and dentin. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995;80:710-9

Narhi M, Jyvasjarvi E, Virtanen A, Huopaniemi T, Ngassapa D, Hirvonen T. Role of intradental A- and C-type nerve fibres in dental pain mechanisms. *Proc Finn Dent Soc.* 1992; 88 suppl 1:507-16

Ng YL, Glennon JP, Setchell DJ, Gulabivala K. Prevalence of and factors affecting post obturation pain in patients undergoing root canal treatment. *Int Endod J* 2004;37:381-91

Nixdorf DR, Moana-Filho EJ, Law AS, McGuire LA, Hedges JS, John MT. Frequency of nonodontogenic pain after endodontic therapy: A systematic review and meta analysis. *J Endod.* 2010; 36(9): 1494-8

Oguntebi BR, DeSchepper EJ, Taylor T, White C, Pink F. Postoperative pain incidence related to the type of emergency treatment of symptomatic pulpitis.

O'Keefe EM. Pain in endodontic therapy: preliminary study. *J endod* 1976. 2(10): 315-19

Okeson JP. *Bell's Orofacial Pain*. 5th ed. Quintessence Publishing Co., Inc. Chicago 1995

Olgart LM, Edwall B, Gazelius B. Neurogenic mediators in control of pulpal blood flow. *J Endod* 1989;15:409-12

Pacheco MA, Teixeira FB, Hargreaves KM, Diogenes A. Prevalence of mechanical allodynia in endodontic patients *J Endod* 2011; 37: e24

Pak JG, White SN. Pain prevalence and severity before, during, and after root canal treatment: a systematic review. *J Endod* 2011;37:429-438

Pelissier T, Alloui A, Caussade F. Paracetamol exerts a spinal antinociceptive effect involving an indirect interaction with 5-hydroxytryptamine₃ receptors: in vitro and in vitro evidence. *J Pharmacol Exp Ther* 1996: 278:8-14.

Raja SN, Campbell JN, Meyer RA. Evidence for different mechanisms of primary and secondary hyperalgesia following heat injury to the glabrous skin. *Brain* 1984; 107; 1179-1188

Reddy SA, Hicks ML. Apical extrusion of debris using two hand and two rotary instrumentation techniques. *J Endod* 1998; 24: 180-3

Rogers MJ, Johnson BR, Remeikis NA, BeGole EA. Comparison of effect of intracanal use of ketorolac tromethamine and dexamethasone with oral ibuprofen on post treatment endodontic pain. *J Endod*, 1999. 25(5): 381-84

Ruiz-Hubard EE, Gutman JL, Wagner MJ. A quantitative assessment of canal debris forced periodically during root canal instrumentation using two different techniques. *J Endod* 1987;13; 554-8

Ryan J, Jureidini B, Hodges J, Baisden M, Swift J, Bowles W. Gender differences in analgesia for endodontic pain. *J Endod* 2008;34: 552-556

Samuelsson B, Hammarstrom S. Nomenclature of leukotrienes. Prostaglandins. 1980 19(5) 645-8

Samuelsson BJ. Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. *Science* 1983 220(4597): 568-75

Sessle B. Neurophysiology of orofacial pain. *Dent Clin North Am* 1987; 31: 595-613

Sessle BJ. Acute and chronic craniofacial pain: Brainstem mechanisms of nociceptive transmission and neuroplasticity and their clinical correlates. *Cait Rev Oral Biol Med* 2000; 11:57-91

Shepherd MA, Nadanvosky P, Sheiham A. The prevalence and impact of dental pain in 8 year old school children in Harrow, England. *Br Dent J* 1999; 187:38-41

Siqueira JH, Rocas IN, Rosado AS. Investigation of bacterial communities associated with asymptomatic and symptomatic endodontic infections by denaturing gradient gel electrophoresis fingerprinting approach. *Oral Microbial Immunol* 2004; 19: 363-370

Sjogren U, Figdor D, Spangberg L, Sundqvist G. The antimicrobial effect of calcium hydroxide as a short-term intracanal dressing. *Int Endod J* 1991;24:119-25

Sjoqvist O. Studies on pain conduction in the trigeminal nerve: A contribution to the surgical treatment of facial pain. *Acta Psychiatrica Scand Suppl* 1938: 17:1-139

Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, et al. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus [published erratum appears in *Arch Intern Med* 2005;165:55]

Spinas GA, Bloesch D, Keller U, Zimmerli W, Cammisuli S. Pretreatment with ibuprofen augments circulating tumour necrosis factor, interleukin-6 and elastase during acute endotoxemia. *J Infect Dis* 1991;163:89

Sunakawa M, Chiang C, Sessle GJ. Jaw electromyographic activity induced by the application of algogenic chemicals to the rat tooth pulp. *Pain* 1999; 80: 493-501

Swift JQ, Hargreaves KM. Pentazocine analgesia: is there a niche for Talwin Nx? *Compendium*, 1993. 14(8) 1048, 1050 passim; quiz 1060

Takahashi K. Microbiological, pathological, inflammatory, immunological and molecular biological aspects of periradicular disease. *Int Endod J* 1998;31:311-25

Taylor H, Curran NM. *The Nuprin Pain Report*. New York, NY: Lou Harris 1985

Torabinejad M, Ketterting JD, McGraw JC, Cummings RR, Dwyer TG, Tobias TS. Factors associated with endodontic interappointment emergencies of teeth with necrotic pulps. *J Endod* 1988;14:261-6

Torabinejad M, Cymerman J, Frankson M, Lemon R, Maffio J, Schilder H. Effectiveness of various medications on postoperative pain following complete instrumentation. *J Endod* 1994; 20:345-354

Torabinejad M, Dorn SO, Eleazer PD, Frankson M, Jouhari B, Mullin RK, Soluti A.
Effectiveness of various medications on postoperative pain following root canal obturation. *J Endod* 1994;20:427-31

Trope M. Flare-up rate of single-visit endodontics. *Int Endod J* 1991;24:24-6

Trowbridge HO. Review of dental pain – histology and physiology. *J Endod* 1986;12:445-52

Urquhart E. Analgesic agents and strategies in the dental pain model. *J Dent* 1994; 22(6):336-41

Vane JR, Botting RM. Mechanism of action of anti-inflammatory drugs. *Int J Tissue React* 1998 20(1) 3-15

Walton R, Fouad A. Endodontic inter-appointment flare-ups: a prospective study of incidence and related factors. *J Endod* 1992;18:172-7

Wells LK, Drum M, Nusstein J, Reader A, Beck M. Efficacy of ibuprofen and ibuprofen/acetaminophen on postoperative pain in symptomatic patients with a pulpal diagnosis of necrosis. *J of Endod* 2011;37: 1608-12

Willis W. The Pain system: the neural basis of nociceptive transmission in mammalian nervous system. basel: Karger, 1985

Woolfe C. Windup and central sensitization are not equivalent. *Pain* 1996; 66:105-108

Woolfe C. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. *Proc Natl Acad Sci USA* 1999; 96: 7723-7730

Young CL, Strand V, Altman R, Daniels S. A phase 2 study of naproxen submicron particle capsules in patients with post-surgical dental pain. *Adv Ther* 2013 Oct;20(10):885-96

Zahrowski JJ. Good evidence supports acetaminophen as an effective and safe reliever of acute postoperative pain. *J Am Dent Assoc* 2010;141:45-6

APPENDIX #1

Consent form

CONSENT FORM

Local Anesthesia and Analgesics in Post-Operative Endodontic Pain

You are invited to participate in a research study of the effect of different pain medications and local anesthetics for tooth pain after beginning a root canal. You were selected as a possible participant because you have tooth pain and are in need of root canal treatment for your tooth. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by Walter Bowles DDS PhD, Steven Wiswall DDS, and Riley Lewis DDS, Division of Endodontics at the University of Minnesota School of Dentistry. It is funded by the Endodontics division, to examine methods for pain relief after starting a root canal.

Study Purpose

The purpose of the study is to determine the best way to treat tooth pain after starting a root canal, by evaluating your pain level before treatment and after treatment when you are given local anesthetic and pain medication. We will provide regular or long-lasting local anesthesia before starting the root canal, and pain medication after the root canal to determine which method(s) provide the best pain relief.

Study Procedures

If you agree to participate in this study, we would ask you to do the following: Evaluate the amount of tooth pain you are having (mark on pain scales the level of pain you feel) before and after root canal treatment, after taking pain medication, and during the following day. You will be given either local anesthetic or long-acting local anesthetic before the root canal, and you will be given two doses of pain medication to take during the first day. After evaluating your tooth pain level at several time points each day till the end of the day following the root canal, you will then need to mail the forms back to the University in a pre-addressed, postage paid envelope.

The root canal procedure is the standard treatment for this type of tooth pain and the medications given are standard pain medication given to patients reporting tooth pain. Assignment to study groups is randomized and all patients will get anesthetic (local or long acting local anesthetic), take 2 doses of pain medication and fill out pain level forms.

Risks of Study Participation

The study has the following risks: analgesic medication may have a side effect of stomach upset or may cause drowsiness.

Benefits of Study Participation

IRB Code # 1311M45621
Version Date: 10/21/13

There is no direct benefit to the patients enrolled.

Voluntary Nature of the Study

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Contacts and Questions

The researchers conducting this study are Walter Bowles DDS PhD, Steven Wiswall DDS, and Riley Lewis DDS. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact them at 612-624-9900 (Division of ~~Endodontics~~, University of Minnesota School of Dentistry)

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at *Fairview Research Administration, 2344 Energy Park Drive, St. Paul, MN 55108*.

You will be given a copy of this form to keep for your records.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Signature of Subject _____

Date _____

Signature of Person Obtaining Consent _____

Date _____

APPENDIX #2

Second Consent form

CONSENT FORM

Local Anesthesia and Analgesics in Post-Operative ~~Endodontic~~ Pain

You are invited to participate in a research study of the effect of different pain medications and local anesthetics for tooth pain after beginning a root canal. You were selected as a possible participant because you have tooth pain and are in need of root canal treatment for your tooth. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by Walter Bowles DDS PhD, Steven Wiswall DDS, and Riley Lewis DDS, Division of ~~Endodontics~~ at the University of Minnesota School of Dentistry. It is funded by the ~~Endodontics~~ division, to examine methods for pain relief after starting a root canal.

Study Purpose

The purpose of the study is to determine the best way to treat tooth pain after starting a root canal, by evaluating your pain level before treatment and after treatment when you are given local anesthetic and pain medication. We will provide regular or long-lasting local anesthesia before starting the root canal, and pain medication after the root canal to determine which method(s) provide the best pain relief.

Study Procedures

If you agree to participate in this study, we would ask you to do the following: Evaluate the amount of tooth pain you are having (mark on pain scales the level of pain you feel) before and after root canal treatment, after taking pain medication, and during the following day. You will be given either local anesthetic or long-acting local anesthetic before the root canal, and you will be given two doses of pain medication to take during the first day. After evaluating your tooth pain level at several time points each day till the end of the day following the root canal, you will then need to mail the forms back to the University in a pre-addressed, postage paid envelope.

The root canal procedure is the standard treatment for this type of tooth pain and the medications given are standard pain medication given to patients reporting tooth pain. Assignment to study groups is randomized and all patients will get anesthetic (local or long acting local anesthetic), take 2 doses of pain medication and fill out pain level forms.

Risks of Study Participation

The study has the following risks: analgesic medication may have a side effect of stomach upset or may cause drowsiness.

Benefits of Study Participation

IRB Code # 1311M45621

Version Date: 10/21/13

There is no direct benefit to the patients enrolled.

1 of 3

Alternatives to Study Participation

If you do not wish to participate, you may proceed with local anesthetic and root canal treatment.

Study Costs/Compensation

You will not incur any costs due to research participation. The root canal procedure will be charged in the regular manner. The emergency treatment fee (approximately \$175) will not be charged if you decide to participate in the study for your time and inconvenience or, if this fee is covered by other monies, this amount may be credited toward the ~~endodontic~~ treatment fee if you so wish. The emergency fee reduction is pro-rated for partial participation (i.e. if not all pain evaluation forms returned) and will be reduced to approximately half (\$85 credit) if only first 2 pain forms are filled out, and \$15 credit for each of the pain scales filled out at home and returned (6 other forms given in take home packet \$90 credit)

Research Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study dentists know right away.

Confidentiality

The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may, however, be reviewed by departments at the University with appropriate regulatory oversight. Study information will be recorded in the your medical record stating only the study number and that you were given pain medication. To these extents, confidentiality is not absolute. Study data will be encrypted according to current University policy for protection of confidentiality.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This Web site will not include information that could identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Protected Health Information (PHI)

Your PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this

IRB Code # 1310M45821
10/01/2010 10/21/13

Voluntary Nature of the Study

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Contacts and Questions

The researchers conducting this study are Walter Bowles DDS PhD, Steven Wiswall DDS, and Riley Lewis DDS. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact them at 612-624-9900 (Division of Endodontics, University of Minnesota School of Dentistry)

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), you are encouraged to contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at Fairview Research Administration, 2344 Energy Park Drive, St. Paul, MN 55108.

You will be given a copy of this form to keep for your records.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Signature of Subject _____

Date _____


Signature of Person Obtaining Consent _____

Date _____

APPENDIX #3

Pain Scales

FORM #1



UNIVERSITY OF MINNESOTA

Laboratory of Neuropharmacology

School of Dentistry

515 Delaware Street SE

Minneapolis, MN 55455

STUDY: IDS #4497

PATIENT # _____

DATE: _____

TIME POINT: Pre-op (form #1)

CLOCK TIME: _____

Check the box that best describes the amount of pain that you feel now:

☐ 3 = Severe
☐ 2 = Moderate
☐ 1 = Mild
☐ 0 = None

*Place a mark on the line to show the amount of **PAIN** that you feel now:*

No
Pain

Pain As Much As
It Could Be

*Place a mark on the line to show the amount of **PAIN** that you feel now:*

None

Faint

Weak

Mild

Moderate

Strong

Intense

Maximum
Possible

Have you taken any medication since the last report? yes /no

Have you experienced any adverse effects or benefits from this medication?
yes /no
If yes, please describe.